IMPACT OF TRAUMATIC BRAIN INJURIES ON PARTICIPATION IN DAILY LIFE AND WORK: RECENT RESEARCH AND FUTURE DIRECTIONS

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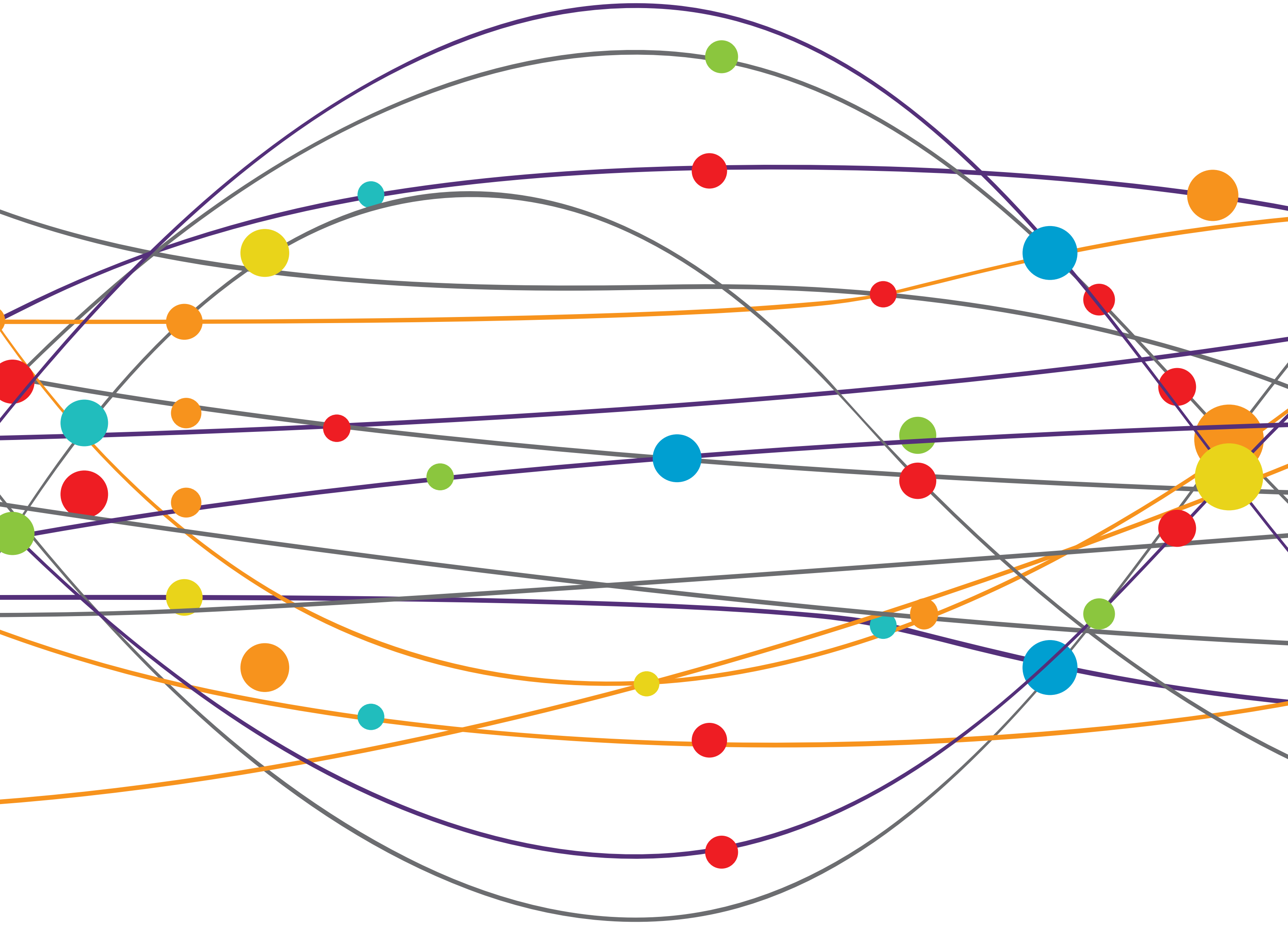

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EDITORIAL
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Editorial: Impact of Traumatic Brain Injuries on Participation in Daily Life and Work: Recent Research and Future Directions

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Keywords: brain injury, functioning, disability, long-term outcomes, rehabilitation, healthcare services

Editorial on the Research Topic

Impact of Traumatic Brain Injuries on Participation in Daily Life and Work: Recent Research and Future directions

A large proportion of individuals with traumatic brain injuries (TBI) sustain long-term physical, cognitive, and emotional impairments that have a profound impact on their everyday level of functioning, community participation, and reintegration (1). Participation in daily life activities and work is identified as one of the most important outcomes of TBI-rehabilitation by patients, their families and healthcare professionals. Identifying predictors for long-term participation is complicated, as there is a complex interaction between several influential factors (2). For example, motor and cognitive deficits appear to have significant impact on participation in the early stages, whereas personal, emotional and social factors play a major role in later stages of TBI (3). Injury-specific factors seem to play the largest prognostic role early on, whilst general factors such as resilience, access to social support, and degree of pre- and co-morbid psychological problems, play a greater role in long-term adjustment (4).

There are a limited number of well-designed TBI studies examining determinants of participation by the individuals with TBI, effective rehabilitation and community re-entry programs, and long-term outcomes. Rehabilitation studies from different countries are required to allow a better understanding of sociopolitical and cultural variation in patient needs and service delivery.

This e-book comprises 12 original research articles and two reviews from Australia, Canada, China, Denmark, France, Netherlands, Norway, and USA. The materials provide insights into the impact of TBI on physical, cognitive, emotional, behavioral and psychosocial functioning, participation in daily life activities and work, driving behavior, vocational rehabilitation, the role of peer support groups, financial compensation following TBI, and classification of health-related rehabilitation services.

The book opens with an original article by Wardlaw et al., which assessed the association of resilience, demographic, injury-related, cognitive, emotional, and family factors with participation following TBI. The study demonstrated that, across the full spectrum of injury severity, and persisting disabilities, resilience can impact on community reintegration many years post injury. Understanding the role of resilience can promote optimistic and hopeful treatment approaches.

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The article by Shao et al. found that patients with mild TBI had reduced cortical thickness in the left entorhinal cortex while increased cortical thickness in the left precuneus cortex and right lateral occipital cortex. Female patients also had an increased cortical thickness in the left caudal anterior cingulate cortex compared to males. Increased cortical thickness was positively related to post-traumatic stress complaints in female patients. Sex differences in cortical thickness may be used as a neuroimaging phenotype for investigating clinical profiles of mild TBI.

In their review article, Polinder et al. discussed current evidence and controversies concerning the use of the terms post-concussion symptoms vs. syndrome, its diagnosis, etiology, prevalence, assessment, and treatment in both adults and children. The authors highlighted that post-concussion symptoms are dependent on complex interactions between somatic, psychological, and social factors, and that treatment is variable, and primarily directed at symptom relief, rather than at modifying underlying pathology.

An original article by Tibæk et al. investigated return to work in young persons (<30 years) with acquired brain injury, over a 10 years period. About one third had not achieved stable return to work and had much lower odds compared to controls for stable work attachment. No improvements in return to work were obtained after 2–5 years. Given the economic and social benefits of work, this result presents a major rehabilitation challenge.

Dornonville de la Cour et al. described a multidisciplinary, holistic and individually tailored vocational rehabilitation (VR) program for individuals with mild traumatic brain injury (mTBI). Both number of hours at work and RTW-status improved, with 97% having returned to work after VR. Shorter time since injury and male sex predicted a greater increase in working hours. The results suggest that individuals with mTBI may improve employment outcomes even years after injury with vocational rehabilitation support, and these preliminary findings demonstrate the need for further research into VR.

Winter et al. investigated potential mediation of variables influencing employment status following TBI in U.S. military veterans. Pain predicted employment status, but its effect was attenuated by physical health and functioning. Physical functioning effects were also attenuated when depressive symptoms were accounted for. This study illustrates the value of mediation analyses in yielding insights into predictors of employment status after TBI, particularly in tertiary prevention of poor TBI outcomes.

Howe et al. examined trajectories of employment probability up to 10 years following moderate-to-severe TBI, and found that overall probability of employment remained relatively stable at ∼50% between 1-, 2-, 5-, and 10 years. Male gender, individuals in a partnered relationship at the time of injury, those employed at the time of injury, in a white-collar profession, and participants with higher acute injury severity had higher employment probability trajectories across the follow-up times. Regular follow-up is recommended for patients at risk of long-term unemployment.

Forslund et al. described longitudinal trajectories of overall disability assessed with the Glasgow Outcome Scale Extended (GOSE) in the first 10 years after moderate-to-severe TBI. They found that 37% of survivors experienced deterioration in disability levels between 5- and 10-year follow-ups, supporting the concept of TBI as a chronic health condition. Younger age, pre-injury employment, male gender, white collar occupation and shorter duration of post-traumatic amnesia are prognostic of better long-term global outcomes. Intensive and tailored rehabilitation may be required to counteract negative developments in disability levels.

The original article by Soendergaard et al. investigated neurobehavioral difficulties following severe brain injury as reported by both the survivor and their close family member using the St Andrew's-Swansea Neurobehavioral Outcome Scale (SASNOS). One fourth of the patients reported problems in Interpersonal Behavior and Cognition. Significant associations were found between proxies' reports and time since injury, cohabitant status, and the patient's score on the GOSE, and differences were seen between patient and proxy ratings. The problems reported by survivors and their proxies can affect the survivor's ability to reintegrate and participate in activities of daily living, emphasizing need for systematic assessment and tailored intervention.

In their prospective 8-years outcome study from a Parisian cohort with severe TBI, Ruet et al. showed that cognitive complaints were common, with ∼70% reporting impaired mental speed, concentration and memory. Comparably, 30–40% had somatic complaints, and about one fourth experienced emotional distress. About half were in productive work. Only 20% showed good recovery on the GOSE, indicating that persisting impairments interfere with social integration and participation 8 years after injury.

In the same Parisian cohort, Bayen et al. investigated the relationship between compensation amounts and injury outcomes in litigants at 4 and/or 8 years after injury. Compensation amounts were positively associated with severity of disability and cognitive impairment, and with care time provided by caregivers. No association was seen with gender, age, education, motor/balance impairment, return to work status, mood or caregiver's subjective burden.

McKerral et al. explored driving behavior after TBI in individuals whose drivers' licenses had been suspended and reinstated following rehabilitation compared with individuals with TBI who did not have any suspension, and with non-injured controls. The study documents that the demerit points in official driving records increase significantly after a TBI. The suspended individuals reported lower level of verbal aggression and driving related errors compared to controls. Serious traffic accidents were higher post-injury in the suspended groups, and serious accidents increased despite the individuals' self-evaluation of being safe drivers. This underscores the need for careful examination of driving ability after TBI and may suggest need for an even stricter practice.

The original article by Bakmann et al. concerns a particularly vulnerable group of patients with acquired brain injury, namely adolescents and young adults. In addition to neurological and cognitive impairment, they are faced with issues concerning education, job, family, and social life. The paper emphasized how young survivors of brain injury benefit socially and psychologically from meeting like-minded peers in a peer support group, and how this may promote psychosocial recovery in adolescents and young adults with ABI.

The last review article by Røe et al. applied the International Classification System for Service Organization in Health-related Rehabilitation (ICSO-R) in a review of randomized intervention trials targeting moderate to severe traumatic brain injured persons in the post-acute phase. Few studies targeted these factors directly in their designs and analysis. However, service provision and delivery often varied between intervention arms in the studies, which could confound outcome evaluations. More standardized reporting of key factors of service provision and delivery in rehabilitation trials is needed.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Psychological Resilience Is Associated With Participation Outcomes Following Mild to Severe Traumatic Brain Injury

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Traumatic brain injury (TBI) causes physical and cognitive-behavioral impairments that reduce participation in employment, leisure, and social relationships. Demographic and injury-related factors account for a small proportion of variance in participation post-injury. Personal factors such as resilience may also impact outcomes. This study aimed to examine the association of resilience alongside demographic, injury-related, cognitive, emotional, and family factors with participation following TBI. It was hypothesized that resilience would make an independent contribution to participation outcomes after TBI. Participants included 245 individuals with mild-severe TBI [$M_{age} = 44.41$, $SD_{age} = 16.09$; post traumatic amnesia (PTA) duration *M* 24.95 days, *SD* 45.99] who completed the Participation Assessment with Recombined Tools-Objective (PART-O), TBI Quality of Life Resilience scale, Family Assessment Device General Functioning Scale, Rey Auditory Verbal Learning Test, National Adult Reading Test, and Hospital Anxiety and Depression Scale an average 4.63 years post-injury (*SD* 3.02, *R* 0.5–13). Multiple regression analyses were used to examine predictors of PART-O scores as the participation measure. Variables in the model accounted for a significant 38% of the variability in participation outcomes, $F_{(13,211)} = 9.93$, $p < 0.05$, $R^2 = 0.38$, adjusted $R^2 = 0.34$. Resilience was a significant predictor of higher participation, along with shorter PTA duration, more years since injury, higher education and IQ, and younger age. Mediation analyses revealed depression mediated the relationship between resilience and participation. As greater resilience may protect against depression and enhance participation this may be a focus of intervention.

Keywords: traumatic brain injury, TBI, resilience, participation, depression, anxiety

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INTRODUCTION

Following traumatic brain injury (TBI), participation in employment, education, leisure, and relationships is often significantly reduced, leaving individuals substantially less integrated in their communities (1–4). As a result, many individuals spend increased time at home, straining family and other relationships (5). Given that TBI occurs commonly during young adulthood (6), participation deficits coincide with a critical period of development in which individuals are completing education, establishing a vocation, leaving home, and forming important lifelong relationships. Failure to attain these goals may profoundly impact their sense of self, mental health and general well-being. Reduced participation often extends beyond the acute recovery period and continues to be associated with poorer quality of life up to two decades after injury (7). Arguably participation in these life roles, including employment, education, leisure and relationships, represents one of the most important and objective indicators of injury outcomes.

Numerous variables have been associated with participation outcomes post-TBI, including injury-related and demographic variables as well as post-injury environmental and personal factors. Injury severity, cognitive difficulties, and limb injuries with related pain and impact on mood, affect an individual's ability to engage socially and often present significant barriers to education and employment (8–16). Injury severity is a particularly well-researched predictor of participation outcomes, with duration of post traumatic amnesia (PTA) having the most robust association (17–21). With respect to demographic factors, younger age, higher premorbid education level, higher premorbid IQ, and being employed prior to injury have all been associated with better participation outcomes (10, 22–29). Notably, older age at injury has been found to predict both worse participation overall as well as progressively worsening participation over time (10). Although gender does not appear to be directly associated with participation (30), it may have an indirect association, for example through mood and pre-injury education (14). Post-injury psychological functioning, particularly depression and anxiety, are also important predictors of participation outcomes (10, 12, 31–33). The impact of family functioning on participation is thought to be both direct, and through association with emotional well-being (34, 35).

Due to this broad range of factors influencing outcome, research has moved toward a multivariate approach to prediction of participation outcomes following TBI (24, 36–38). These models contribute to a more comprehensive understanding of participation outcomes; however, the average amount of variance accounted for by predictive models is around 30% (21). This suggests there are additional predictive factors yet to be identified. One such factor that has increasingly gained scholarly recognition, due its positive association with quality of life and well-being outcomes among different clinical populations, is resilience.

Resilience has been conceptualized as a process of adaptation to adversity or the ability to bounce back after trauma or adversity. Resilience arguably influences the extent to which a person is able to resume important life roles after an injury. Resilience may impact participation outcomes directly through facilitating or promoting return to normal life or the development and achievement of new life goals (39), and indirectly through its effects on improved well-being, quality of life and psychological adjustment. Participating in employment, education, leisure, and relationships represent fundamental areas of participation. Resilience has been positively associated with physical and emotional well-being in individuals with cancer (40), Parkinson's disease (41), diabetes (42), chronic spinal cord injury (43), multiple sclerosis, spina bifida, stroke, and posttraumatic stress disorder (44, 45). There has been less resilience research in TBI, with only one study to date examining the association between resilience and participation. Notably, it has been suggested that the study of resilience after TBI poses a distinct challenge, in that the skills characteristically associated with resilience are typically impaired after TBI (45–47). For example, resilience requires emotional stability, a positive outlook, good problem-solving skills and social perception (47); however, TBI is commonly associated with impaired executive functioning (48, 49), irritability and aggression (50, 51), depression (33, 45), and difficulties with social perception (52).

The little research that has focused on resilience after TBI has been largely limited to patients with mild TBI, in whom no studies have examined impact on participation. In this group, greater resilience has been associated with less reporting of post-concussional and post-traumatic stress symptoms (53–55), reduced fatigue, insomnia, stress, and depressive symptoms, as well as better quality of life (56). One study found that greater pre-injury resilience was significantly associated with greater post-concussion symptom severity 1 month post-injury (57), perhaps reflecting insufficient time for participants to "bounce back" (44), or overrating of pre-injury resilience levels, a phenomenon known as the "Good Old Days"(58).

Only three studies have examined resilience in individuals with moderate to severe TBI, of which one examined an association with participation. Marwitz et al. (39), conducted a large ($n = 195$) longitudinal study and found that resilience was significantly associated with participation over the first 12 months post-injury (39). Other studies have associated higher resilience in individuals with moderate to severe TBI with fewer depressive and anxiety symptoms, better emotional adjustment, use of task oriented coping and greater social support (44, 45). However, one of these studies used a sample of individuals who were actively seeking help with adjusting to changes post-injury, possibly biasing the sample toward those experiencing greater adjustment problems (45).

The aim of the present study was to examine the relative association of resilience, as well as demographic, injury-related, cognitive, emotional, and family factors with participation (productivity, social relations and leisure) following mild to severe TBI. To the best of our knowledge, this is the first study to examine the association between resilience and participation outcomes more than 12 months after mild to severe TBI. This critically extends previous research by examining the impact of resilience across the spectrum of TBI severity, from mild to severe, and how this association influences outcomes beyond the acute post-injury period. It was hypothesized that resilience would make an independent contribution to participation after TBI, in a model that would include demographic variables (gender, age, pre-morbid IQ, education, pre-injury employment), injury variables (injury severity, cognitive functioning, limb injury, time since injury) and post-injury personal and environmental factors (depression, anxiety, family support).

MATERIALS AND METHODS

This research was approved by the Epworth Human Research Ethics Committee and Monash University Human Research

TABLE 1 | Demographic, injury, personal, and environmental characteristics of participants with traumatic brain injury ($n = 245$).

Variable	*N*	*M*	*SD*	Range
Age at interview	245	44.41	16.09	17–78
Age at injury	245	40.16	16.48	16–77
Education (years)	245	13.52	3.09	6–27
Estimated FSIQ	239	109.02	7.53	88–127
Time since injury (years)	245	4.63	3.02	0.05–13
GCS	231	9.82	4.25	3–15
Mild (13–15)		42%		
Moderate (9–12)		16.9%		
Severe (3–8)		41.1%		
Duration of PTA (days)	234	24.95	45.99	0–455
<7 days		7.3%		
7–28 days		17.9%		
>28 days		74.8%		
Gender	245			
Male	180	73.5%		
Female	65	26.5%		
Employed before Injury	245			
Yes	217	88.6%		
No	28	11.4%		
Limb injury	244			
None	91	37.4%		
Minor	25	10.2%		
Moderate	63	25.8%		
Major	65	26.6%		

FSIQ, Full Scale IQ; GCS, Glasgow Coma Scale; PTA, Post traumatic Amnesia.

Ethics Committee. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Participants

The sample for this study was drawn from a larger prospective longitudinal head injury outcome study conducted at Epworth Hospital in Melbourne, Australia. Inclusion criteria for the current study included being aged 16 years or over and having a history of TBI sustained at least 3 months previously. Exclusion criteria included inadequate English or cognitive capability to complete the study measures, other pre-injury or post-injury neurological conditions or severe psychiatric disturbance (e.g., psychosis). Two-hundred and forty-five individuals met the eligibility criteria and consented to the study. There were no significant differences in age, gender, duration of PTA or GCS score between the study sample and patients who were admitted to the Epworth Hospital for rehabilitation and included in the longitudinal study during the same period (May 2004–July 2016). However, there was a significant difference in total years of education, with study participants having greater years of education (M 13.52 SD 3.09) compared to non-participants [*M* 10.24 *SD* 4.14; $t_{(386)} = -8.7, p < 0.001$].

As shown in **Table 1**, 73.5% of the sample were males ($M = 43.50$ years, $SD = 15.55$ years) and 26.5% were females ($M = 46.95$ years, $SD = 17.25$ years). The mean age of participants was 44.41 years ($SD = 16.09$, $R = 17$–78 years), and the majority of participants had sustained a severe TBI, based on PTA duration ($M = 24.95$ days, $SD = 45.99$; $R =$ 0–455) and GCS score ($M = 9.82$, $SD = 4.25$; $R = 3$–15).

Measures and Procedures

Participants from the longitudinal head injury outcome study database were telephoned and invited to complete research interviews for the present study, a collaboration with Sherer et al. from TIRR Memorial Hermann, Houston, Texas, USA, identifying predictive models of TBI outcome (59). Recruitment and interviews occurred between January 2015 and June 2017. Participants were seen in their homes (66.9%) or at the hospital (33.1%) and were reimbursed for their time. The 90-min assessments included measures of mood, lifestyle and participation, and several cognitive measures. Demographic and injury data including gender, age, years of education, pre-injury employment, GCS scores, duration of PTA, and limb injuries were obtained from medical records and interviews.

National Adult Reading Test

National Adult Reading Test (NART) (60). The NART consists of a 50-item word list, which the participant reads aloud. It is a validated as a measure of premorbid intellectual functioning in individuals post TBI (61).

Rey Auditory Verbal Learning Test

Rey Auditory Verbal Learning Test (RAVLT) (62). The RAVLT is a list learning memory task (40). The total words recalled for the five learning trials (RAVLT Trials 1-5) was used, as this has been identified as the most reliable measure (test-retest $r = 0.77$) (63). T-scores were generated (62), with higher scores reflecting better cognitive performance. The RAVLT is sensitive to the cognitive effects of TBI (49, 64).

Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS) (65). The HADS comprises two subscales measuring anxiety and depression. Higher scores are indicative of higher depression and/or anxiety symptoms. The HADS has good internal consistency [Cronbach's $\alpha = 0.83$ anxiety; $\alpha = 0.82$ depression; (66)], and has been found to be a reliable and valid measure of emotional distress in TBI populations (67, 68).

Family Assessment Device General Functioning Scale

Family Assessment Device General Functioning Scale (FAD-12) (69). The FAD-12 is a 12-item subscale of the FAD, recommended for use as an index of family functioning (70). The higher the score, the more problematic the participant perceives the overall family functioning (71). The FAD-12 has good psychometric properties [Cronbach's $\alpha = 0.90$; (72)], and has been validated for use in TBI populations (73, 74).

Traumatic Brain Injury Quality of Life Resilience scale

Traumatic Brain Injury Quality of Life Resilience scale (TBI-QoL Resilience) (75). The TBI-QoL Resilience subscale is one of twenty subscales from the TBI Quality of Life measure. The 10-item measure uses a 5 point Likert scale and the total resilience score represents the individual's standing compared to that of other individuals with TBI (75). There has been limited analysis of the psychometrics of this scale, however, in a sample of military service members with mild TBI, the internal consistency was high [Cronbach's $\alpha = 0.91$; (76)]. It has been suggested that the psychometric properties for the scale are likely to be strong due to the method of validation of the measure (77), which included focus groups, interviews, and patient consultation from individuals with TBI, clinicians, and caregivers of individuals with TBI. Additionally, item pools were tested in a large sample ($n = 675$) and calibrated using item response theory methods.

Participation Assessment With Recombined Tools-Objective

Participation Assessment with Recombined Tools-Objective [PART-O-17; (78)]. The PART-O measures frequency of productivity, "out and about" (e.g., going to the movies) and social relations, with higher scores indicative of greater community participation. The PART-O has been shown to have good construct and concurrent validity and the ability to reliably measure significant differences among individuals with varying levels of participation (79). The Averaged Total Score was used as an indication of overall participation post-injury (1). The PART-O has been shown to be an acceptable measure of participation for individuals with moderate and severe TBI (79) and is recommended for assessing social role participation in the TBI population by the National Institute of Neurological Disorders and Stroke (80).

Data Analysis

A multiple regression analysis using SPSSv.24 (SPSS, Inc., Chicago, IL) was undertaken to assess the extent to which selected variables predicted participation outcomes on the PART-O. Listwise deletion was deemed appropriate for all analyses as the total missing data represented $< 0.3\%$ of responses and was judged to be missing completely at random (MCAR; Little's MCAR $p > 0.05$) (81–83). Sample size requirements for a multiple regression with 13 predictors were met (83). Five univariate outliers were identified (z score $\pm$ 3.29 standard deviations from the mean) (83) but found to be valid clinical cases meeting study inclusion criteria. Furthermore, standardized residuals statistics showed no residuals that were $\pm$ 3.29 standard deviations from the mean, and Cook's Distance had a maximum value of 0.44 (84), indicating that there were likely no cases having an undue influence on the regression model. Assumptions of normality of the dependent variable, multicollinearity, normality, linearity and homoscedasticity of residuals and independence of errors were all met. There was no evidence of multicollinearity: all tolerance values were > 0.10 and all variance inflation factors were < 10 (85). Furthermore, individual examination of the correlation values between independent variables showed none above the 0.80 threshold (85).

Due to extensive research demonstrating PTA to be a more robust reflection of TBI severity and predictor of outcomes (14, 19, 86), PTA rather than GCS was included in the regression model. The following predictor variables were regressed on the outcome variable (PART-O): TBI QoL resilience, age at interview, gender, total years of education, employment status pre-injury, PTA duration, limb injury, premorbid IQ, RAVLT Trials 1-5 score, FAD-12 score, HADS anxiety score, HADS depression score, and years since injury.

Mediation analyses were conducted to explore whether depression and anxiety symptoms mediated the relationship between resilience and participation outcomes. The mediation analyses were conducted using PROCESS v. 2.16 (87), in line with current recommendations in the literature (85, 88, 89).

RESULTS

The multiple regression analysis predicting participation outcomes on the PART-O included 225 participants. In combination, the variables in the model accounted for a significant 38% of the variability in participation outcomes, $F_{(13, 211)} = 9.93, p < 0.05, R^2 = 0.38$, adjusted $R^2 = 0.34$.

Review of coefficients revealed that resilience made a unique contribution and was a significant predictor of participation outcomes ($\beta = 0.17, p < 0.05$). Furthermore, age at interview ($\beta = -0.24$, p <0.01), premorbid IQ ($\beta = 0.21, p < 0.05$), PTA duration ($\beta = -0.20, p < 0.01$), total years of education ($\beta = 0.18, p < 0.05$), and years since injury ($\beta = 0.11, p < 0.01$) significantly predicted participation outcomes. The raw (B) and standardized (β) regression coefficients of the predictors, together with their squared semi-partial correlations indicating the unique variance predicted by each independent variable, are shown in **Table 2**. Participants' participation scores increased with higher resilience, higher years of education, higher premorbid IQ, greater years since injury, shorter PTA duration, and younger age. Gender, limb injury, employment status pre-injury, cognitive performance on the RAVLT, HADS anxiety and HADS depression, and family functioning were not significantly associated with participation outcomes.

The finding that depression and anxiety were not uniquely significant predictors of participation outcomes was unexpected. Given the association of resilience with depression and stress in previous studies (45, 53–56), as well as the findings of previous studies that depression and anxiety were associated with participation outcomes (10, 12, 31–33), it was considered important to further investigate their role, as potential mediators. Indeed, depression scores had medium to strong correlations with both participation ($r = -0.39, p < 0.01$) and resilience ($-0.64, p < 0.01$; See **Table 3** for correlations). Anxiety had a weak correlation with participation ($r = -0.28, p < 0.01$), but also had a strong correlation with resilience ($r = -0.62, p < 0.01$). In order to assess whether depression mediated the relationship between resilience and participation outcomes, PROCESS v. 2.16 (87) was used with the default setting of 1000 bootstrapped samples on a model that included 243 participants. The relationship between resilience and participation outcomes was significant, $R = 0.37, R^2 = 0.13, F_{(1, 241)} = 37.15, p < 0.01$. The inclusion of depression in the model representing the relationship between resilience and participation outcomes was also significant, $R = 0.42, R^2 = 0.18, F_{(2, 240)} = 26.30, p < 0.01$. The indirect effect of resilience on participation outcomes via depression was significant $\beta = 0.01$, 95%, BCa CI [0.006, 0.02]. Refer to **Figure 1.**

PROCESS v. 2.16 (87) was also used to assess whether anxiety was a mediator of the relationship between resilience and participation outcomes ($n = 244$). The relationship between resilience and participation outcomes was significant, $R = 0.37$, $R^2 = 0.13$, $F_{(1,242)} = 37.41$, $p < 0.01$. The inclusion of anxiety in the model representing the relationship between resilience and participation outcomes was also significant, $R = 0.37$, $R^2 = 0.14$, $F_{(2,241)} = 19.38$, $p < 0.01$. However, the indirect effect of resilience on participation outcomes via anxiety was not significant $\beta = 0.003$, 95%, BCa CI [−0.002,0.009]. Refer to **Figure 2.**

TABLE 2 | Unstandardized and standardized regression coefficients predicting participation outcomes and squared semi-partial correlations ($N = 225$).

Variable	B (SE-B)	β	sr^2
DEMOGRAPHIC VARIABLES			
Age at interview	−0.008 (0.024)	−0.240**	0.04
Gender	−0.041 (0.069)	−0.035	0.00
Premorbid IQ	0.015 (0.005)	0.217**	0.03
Total years education	0.032 (0.011)	0.186**	0.02
Pre-injury employment	−0.003 (0.094)	−0.002	0.00
INJURY VARIABLES			
PTA	−0.003 (0.001)	−0.203**	0.04
Limb injury	0.003 (0.024)	0.007	0.00
Years since Injury	0.020 (0.010)	0.116*	0.04
RAVLT Trials	0.003 (0.003)	0.087	0.00
POST-INJURY PERSONAL AND ENVIRONMENTAL VARIABLES			
Resilience	0.012 (0.006)	0.173*	0.01
Depression	−0.015 (0.011)	−0.118	0.00
Anxiety	−0.001 (0.010)	−0.008	0.00
Family functioning	0.075 (0.056)	−0.085	0.00

*The dependent variable was Participation outcomes. $R^2 = 0.38$, Adjusted $R^2 = 0.34$. SE-B = standard error of unstandarised beta; sr^2 = the squared semi-partial correlation indicating the unique variance predicted by each independent variable; PTA, Post traumatic amnesia; RAVLT Trials, Rey Auditory Verbal Learning Test Trials 1-5. *$p < 0.05$. **$p < 0.01$.*

DISCUSSION

The current study explored the association of resilience, alongside demographic, injury-related, emotional and environmental factors, with participation outcomes following TBI. A broad view of participation was taken, including social relationships and leisure activities, as well as productivity. The hypothesis that resilience would make an independent contribution to participation outcomes was supported, in a model that collectively predicted 38% of the variance in participation. In combination, higher resilience, higher years of education, higher premorbid IQ, greater time since injury, shorter PTA duration, and younger age, significantly predicted increased participation. Mediation analyses demonstrated that depression mediated the relationship between resilience and participation, however, anxiety was not a significant mediator of this relationship.

Resilience made a unique, albeit modest, contribution to participation outcome an average of 4 years and up to 13 years post injury. This suggests that despite the presence of significant and persisting disabilities in this mild to severe sample, personal qualities such as resilience may impact on the individual's capacity to reintegrate into the community. This confirms previous research finding an association between resilience and participation following TBI (39), and extends current knowledge by demonstrating this association beyond 12 months post-injury. Survivors with more resilient profiles also showed better emotional adjustment, which is consistent with previous research in similar samples (39, 44, 45). Exploratory mediation analyses demonstrated that depression was a significant mediator of

TABLE 3 | Correlations between demographic, injury, cognitive, personal, and participation variables.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Participation	–													
2. Limb injury	−0.09	–												
3. Age	−0.16**	−0.06	–											
4. Gender	−0.02	−0.08	0.11*	–										
5.Total years education	0.36**	−0.03	−0.01	0.06	–									
6. Pre-injury employment	0.04	−0.03	−0.13*	−0.27**	0.04**	–								
7. PTA	−0.17**	0.03	−0.12*	−0.09	0.06	0.11*	–							
8. RAVLT Trials 1-5	0.19**	−0.04	0.32**	0.20**	0.23**	−0.03	−0.15*	–						
9. Pre-morbid IQ	0.31**	−0.21**	0.24**	0.08	0.48**	0.03	0.05	0.37**	–					
10. Years since injury	0.23**	−0.17**	−0.05	0.02	0.02	0.05	−0.05	0.05	0.11*	–				
11. Resilience	0.34**	−0.08	0.00	−0.08	0.09	−0.00	0.00	0.02	0.06	0.17**	–			
12. Depression	−0.39**	0.13*	0.02	0.09	−0.24**	−0.05	−0.02	−0.19**	−0.12*	−0.24**	−0.64**	–		
13. Anxiety	−0.28**	0.11*	−0.08	0.12*	−0.19**	−0.08	−0.06	−0.09	−0.13*	−0.14*	−0.63**	0.65**	–	
14. Family functioning	−0.29**	0.08	0.09	−0.05	−0.16*	0.000	0.02	−0.03	−0.08	−0.07	−0.38**	0.45**	0.37**	–

*PTA, Post traumatic amnesia; RAVLT Trials, Rey Auditory Verbal Learning Test Trials 1-5. *$p < 0.05$; **$p < 0.01$.*

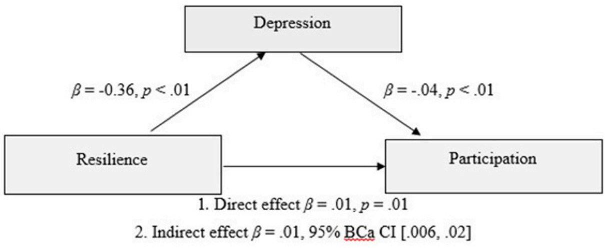

FIGURE 1 | Model of resilience as a predictor of participation outcomes, mediated by depression scores of the participant.

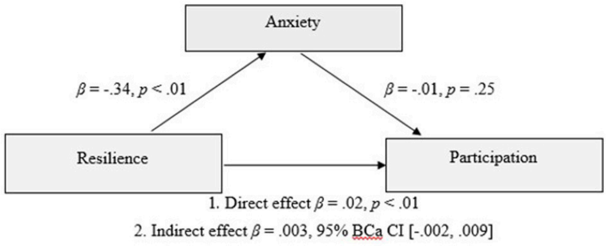

FIGURE 2 | Model of resilience as a predictor of participation outcomes, mediated by anxiety scores of the participant.

the relationship between resilience and participation outcomes. Higher resilience may be a protective factor against depression which in turn affects levels of participation. Further, given the average time since injury was 5 years, this study suggests that the protective influence of resilience on depression may not be limited to the acute post injury period. Anxiety was not a statistically significant mediator of the relationship between resilience and participation. The reason for this finding is unclear but suggests that symptoms of depression and anxiety may interact somewhat differently with participation outcomes in individuals with TBI. Some support for this notion can be inferred from studies which have found employment outcomes to be associated with depression but not anxiety in TBI samples (90, 91). Further, given findings from previous research showing the association between resilience and anxiety is somewhat tempered by time post injury (39), it is also possible that any mediating effect of anxiety may be restricted to the acute post injury period.

There has been only one published study of a resilience-based intervention in the context of TBI (92, 93). This study examined the effectiveness of a psychoeducational and skill-building intervention, the "Resilience and Adjustment Intervention," using a two-arm, parallel, randomized, controlled trial. Individuals who received the intervention showed a significant increase in resilience, however, this was not maintained at 3-months follow-up. It is important to acknowledge that resilience based interventions inherently assume that resilience is a construct that is modifiable and amenable to intervention, however, it remains debatable whether resilience may in fact be a stable trait.

The efficacy of interventions may also be impacted by cognitive impairments, which impede the capacity to take in, remember and follow through with the effects of therapy (45–47). Nevertheless, recent studies have demonstrated that individuals with TBI can benefit from psychological therapy that is adapted for their cognitive impairments (86). Moreover, TBI-specific treatment plans focused on building psychological strengths such as resilience early in the rehabilitation process, could potentially serve to circumvent the development of anxiety and depression and thereby enhance outcomes. Screening for resilience early in the rehabilitation process could also be used to identify individuals at risk of negative emotional responses. Screening processes may be further refined by previous research in this area, which has shown lower levels of resilience post TBI to be associated with being unemployed pre-injury, a lower level of education, being unmarried, being of minority race and having greater levels of disability (39).

These findings further highlight the importance of using multivariate models to identify the complex range of factors that combine to impact on outcome (24, 36–38, 94). The fact that they accounted for a relatively modest amount of variance, may reflect the complexity of the participation construct, including productivity, out and about/leisure, and social relations. Indeed, multivariate models specially examining employment outcomes have found that PTA, age, pre-injury employment, and physical, cognitive, and behavioral disability have predicted 60% or more of the variance in employment outcomes post-TBI (4, 12, 18, 19, 21). It is plausible that certain variables may be more strongly related to certain domains than others. However, as all three domains are inter-related and impact survivors' well-being and quality of life, it is important to study them in combination.

Of the demographic variables, age, pre-morbid IQ, and education contributed significantly to the prediction of participation. Consistent with previous research, younger individuals with higher IQ and higher education were found to have higher participation (10, 14, 22, 28, 29, 95–98). It is possible that increased participation with younger age may be related to improved mobility and physical capabilities in youth compared to the elderly (22, 28, 99, 100). It is also plausible that effects of normal aging may have also contributed to the lower PART-O scores, given older individuals are less likely to be engaged in work or study (10). Future research using a matched control sample would be of benefit to examine the trajectory in scores with normal aging. Higher education has been associated with better outcomes post TBI in previous research, possibly demonstrating the impact of cognitive reserve (101, 102). The cognitive reserve hypothesis postulates that individual differences in cognitive processes or neural networks allow some people to cope better with pathology from disease or brain damage (103). Higher education has been identified as a key source of cognitive reserve (102).

Duration of PTA emerged as the most significant predictor of participation, of the injury-related variables, ahead of current memory performance on RAVLT. This is consistent with previous research showing PTA duration to be a significant predictor of various outcome variables, including return to employment, functional independence, independent living, and cognitive function (14, 18–21, 97, 104). Considering that the average years post-injury in the study sample was 5 years, and extended up to 13 years, our results demonstrate that PTA remains a strong predictor of outcome even many years post-injury. Of the other injury-related variables, after controlling for injury severity, greater time since injury was associated with increased participation, as well as higher resilience, lower depression, and lower anxiety. These findings are consistent with longitudinal data showing that depression and anxiety decline gradually after peaking at 12 months post injury (105). Our findings contrast, however, with recent longitudinal data showing a decline in resilience with greater time post moderate to severe TBI (39). However, given that study was restricted to the first 12 months post injury, it is possible that levels of resilience may decrease in the first year after injury as survivors are confronted with numerous physical, cognitive and emotional challenges, but may, begin to increase over time alongside increased self-awareness, adaptive skill development, acquisition of coping skills, and psychological adjustment. Indeed, such processes of adaptation have been shown to continue over many years after injury (12, 106). Finally, limb injury was not a significant predictor, likely because the time elapsed since injury had allowed for recovery. Consistent with this, previous research has found limb injury to be a significant predictor of outcome at one year post injury, but not 5 years post injury (107).

Almost half of the sample reported unhealthy levels of family functioning. Although not a significant predictor of participation in the model, family functioning showed moderate correlations with resilience, depression and anxiety, and participation. This suggests an interplay between personal psychological strength and family support, and is consistent with previous research (44, 108–110). It is unknown whether healthy family functioning enhances an individual's resilience or whether resilient individuals are more satisfied within their family network. It may be the case that injured individuals with higher resilience are received better within the family unit, thus allowing for healthier family functioning. Further research would be of value to clarify how family functioning and resilience may interrelate, and how this may be associated with participation outcomes.

Notwithstanding the significance of identifying resilience as a potential predictor of participation outcomes post-TBI, the current study has certain limitations. It is possible that the sample was biased toward individuals who are generally inclined to be more participatory than others. This sample was also more highly educated than patients admitted for rehabilitation during the same period, which has implications for generalizability. The design of the study was cross-sectional and cannot be used to infer causation. A longitudinal study would be optimal for investigating resilience in conjunction with changes in emotional adjustment and participation outcomes over time in individuals with varying levels of injury severity. A longitudinal study design would also allow researchers to examine the trajectory of resilience over time, and factors that may contribute to resilience, such as psychosocial interventions, improved family support, return to work or increased status at work, development of friendship or intimate relationships. The amount of variance accounted for by the model was modest, suggesting many other variables not examined in this study may also contribute to participation outcomes. Finally, the measure of resilience used for the current study has yet to be fully validated. However, the TBI-QoL resilience scale was developed exclusively for individuals with TBI to address TBI-specific issues that generic measures fail to address (75) and thus was considered most appropriate for the current study.

In conclusion, this is the first large-scale study to examine the association between resilience and participation in a sample of individuals more than 12 months post mild to severe TBI. Whilst most previous predictive studies have focused on return to work, this study took a broader view of participation, using the PART-O as a measure encompassing engagement in social and leisure activities as well as productivity, which represent important contributors to an individual's well-being. The contribution of resilience to the model, although modest, highlights the significance of the person's response to injury. Given that most previous studies of resilience following TBI have focused on mild injuries only, this study extends previous research by demonstrating that, across the full spectrum of injury severity, and even in the presence of significant and persisting disabilities including cognitive impairments, personal qualities such as resilience can impact on the individual's capacity to reintegrate into the community many years post injury. Further, the additional finding that depression mediated the relationship between resilience and participation, suggests that resilience likely influences the probability of developing depressive symptoms, which in turn impacts on participation. Understanding the role of personal factors such as resilience has the potential to create a foundation for treatments that may foster optimistic and hopeful approaches after injury of any severity and enhance long-term survivor participation in society.

AUTHOR CONTRIBUTIONS

JP, MS, CW, and AH contributed to the conception and design of this study. AH and staff from Monash-Epworth Rehabilitation Research Centre collected all data. CW conducted statistical analyses and lead the drafting of the manuscript. AH and JP provided ongoing supervision and consultation for CW. The interpretation of results and content of the discussion was led by CW, in collaboration JP and AH. All authors contributed to editing and reviewing of the manuscript.

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Preliminary Evidence of Sex Differences in Cortical Thickness Following Acute Mild Traumatic Brain Injury

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The main objective of this study was to evaluate sex differences in cortical thickness after acute mild traumatic brain injury (mTBI) and its associations with clinical outcomes. Thirty-two patients with mTBI at acute phase (2.4 ± 1.3 days post-injury) and 30 healthy controls were enrolled. All the participants underwent comprehensive neurocognitive assessments and MRI to assess cortical thickness. Significant sex differences were determined by using variance analysis of factorial design. Relations between the cortical thickness and clinical assessments were measured with the Spearman Correlation. Results revealed that patients with mTBI had significantly reduced cortical thickness in the left entorhinal cortex while increased cortical thickness in the left precuneus cortex and right lateral occipital cortex, compared with healthy controls. The interaction effect of the group × sex on cortical thickness was significant. Female patients had significant thicker cortical thickness in the left caudal anterior cingulate cortex (ACC) than male patients and had higher scores on Posttraumatic stress disorder Checklist—Civilian Version (PCL-C). Spearman correlational analysis showed a significantly positive correlations between the cortical thickness of the left caudal ACC and PCL-C ratings in female patients. Sex differences in cortical thickness support its potential as a neuroimaging phenotype for investigating the differences in clinical profiles of mild TBI between women and men.

Keywords: mild traumatic brain injury, cortical thickness, gender difference, interaction effect, clinical outcomes

INTRODUCTION

Traumatic brain injury (TBI) is an important global health issue, of which 75–90% are classified as mild TBI (mTBI) (1). Although most patients with mTBI become asymptomatic within days to weeks, some develop a series of persistent symptoms that have been called as "persistent post-concussive syndrome." There are several factors associated with those various outcomes, but one of the most controversial and interesting factors is sex (2). Sex differences in outcomes after mTBI have been addressed in lots of studies, of which some found females have a poorer outcome than males (3–8). Another study have found that females have a higher risk of developing epilepsy, suicide, and use more health care services and males have a higher risk for schizophrenia after mTBI (9). While other studies have shown no substantial difference in outcome with regard to sex (10, 11). The effect of sex on outcome after mTBI is less clear. Observation studies may be confounded by many factors, including different symptoms reporting among women and men (7, 12).Therefore, a more objective measurement, such as imaging findings, is crucial in avoiding such bias. Understanding sex differences of brain injury mechanism after mild TBI may change the future diagnostic work-up in patients with mTBI and lead to separate management strategies for patients of different sex.

Sex differences in brain activities after TBI have been reported in recent years. An fMRI study in veterans with TBI reveals that males showed increased functional connectivity between the left orbitofrontal cortex (OFC) and the right mid frontal cortex compared with females. In the meantime, a significant negative association is found on the overall score on the Buss Perry Aggression Questionnaire with functional connectivity between the left OFC and left angular region in male veterans (13). Diffusion tensor imaging (DTI) shows that male patients with mTBI have decreased fractional anisotropy (FA) in the uncinate fasciculus (UF) compared with female patients and was negatively correlated with time to symptom resolution (14). However, there is lack of findings on the cortical thickness alternations following mild TBI. Cortical thickness is an intrinsic biological parameter and should be independent of external factors such as the MRI scanner type, imaging sequence, spatial resolution and/or field strength (15, 16). Sex differences in cortical thickness have been well-documented in healthy adults (17). Cortical thickness alternations are also reported in the chronic phase of various TBI (from vary mild, moderate to more serve TBI) (18–20), there is no study focused on the sex differences in cortical thickness following acute mTBI. Moreover, gender difference in outcomes, favoring females as endogenous neuroprotectants, has been documented in TBI. However, a consistent finding in the research literature on general traumatic experience is that women exhibit twice the rate of the disorder as men, in spite of men experiencing greater lifetime exposure to traumatic events overall (21–23). We hypothesized that there was a significant interaction effect of gender and diagnosis in the traumatic complaints and associated cortical thickness alternations following mTBI.

MATERIALS AND METHODS

Participants

All consecutive patients with non-contrast head CT due to acute head trauma enrolling from the local emergency department (ED) formed the initial population. Inclusion criteria for all mTBI patients were based on the World Health Organization's Collaborating Center for Neurotrauma Task Force (24): (i) Glasgow Coma Scale (GCS) score of 13–15, (ii) one or more/any of the following: loss of consciousness (LOC) for <30 min, posttraumatic amnesia (PTA) for 24 or less hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesions not requiring surgery, (iii) within 1 week after onset of a mTBI, (iv) were aged 16 years or older. Mild TBI patients were excluded for: (1) a history of a previous brain injury, neurological disease, long-standing psychiatric condition, concurrent substance, or alcohol abuse, (2) a structural abnormality on neuroimaging (CT and MRI), (3) intubation and/or presence of a skull fracture and administration of sedatives, (4) the manifestation of mTBI due to medications by other injuries (e.g., systemic injuries, facial injuries, or spinal cord injury), (5) other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), (6) caused by penetrating craniocerebral injury.

Thirty-two patients with mTBI (18 males) and 30 sex-, age-, and education-matched healthy controls (14 males) without neurologic impairment or psychiatric disorders participated in the study. Participants were all right-handed according to the Edinburgh Handedness Inventory (25). All the subjects gave written, informed consent in person approved by a local institutional review board and conducted in accordance with the Declaration of Helsinki.

Image Acquisition

A non-contrast CT scan was performed on all consecutive patients following acute head injury with a 64-row CT scanner (GE, Lightspeed VCT). All the patients with mTBI went through the MRI scans the day they were recruited in the group. The MRI scans were acquired with the use of 3T MRI scanner (GE 750). A custom-built head holder was used to prevent head movements. The MRI protocol involved the high-resolution T1-weighted 3D BRAVO sequence (echo time = 3.4 ms, repetition time = 7.7 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 256 × 256 mm, matrix size = 256 × 256). The presence of focal lesions and cerebral microbleeds was independently determined by experienced clinical neuroradiologists (with 9 and 10 years' experience) who assessed multiple modalities of neuroimaging data acquired at baseline (T1-flair, T2-flair, T2, susceptibility weighted imaging). Any disagreement between these two observers was resolved by consensus. None of patients were with visible contusion lesions using conventional neuroimaging techniques or exhibited cerebral micro-bleeds on SWI.

Clinical Assessments

Clinical assessments were performed within 48 h of MR imaging for all the participants. Based on these previous publications, a limited set of neuropsychological tests were analyzed in the current study, to reduce multiple testing issues. This selection was based on our previous work demonstrating sensitivity to TBI-related alterations to brain structure (26, 27). The following tests were assessed: (i) Trail-Making Test Part A and Digit Symbol coding score from the Wechsler Adult Intelligence Scale III (WAIS-III) to examine cognitive information processing speed (28); (ii) Forward Digit Span and Backward Digit Span from the WAIS-III to assess immediate auditory span, working memory, and executive function (29); (iii) Verbal Fluency Test to assess verbal fluency including language ability, semantic memory and executive function (30); (iv) Posttraumatic stress disorder Checklist—Civilian Version (31). In addition, post concussive symptoms (PCS) were measured with the Rivermead Post-Concussion Symptom Questionnaire (RPCS) (32).

Cortical Thickness Analyses

We used FreeSurfer version 5.3.0 (33) (https://surfer.nmr.mgh.harvard.edu/fswiki) to extract surface-based features from the high-resolution T1-weighted images. The reliability of obtaining cortical thickness measurements from MRI scans has been well validated (15, 34, 35). The high- resolution T1-weighted MR volume for each participant was bias corrected, skull stripped, and segmented into white matter, gray matter, and cerebrospinal fluid before surface-based morphometry (15). Then, we conducted to tessellate the gray-white boundary, perform automated topology correction, and perform surface deformation to locate the gray-white and gray-pial boundaries (36, 37). Cortical thickness was calculated as the closet distance between the gray-white matter boundary and the pial mesh at each vertex on the tessellated surface (37). The surface was then anatomically parcellated by using the Desikan-Killiany atlas into 66 structures (33 structures for each hemisphere) (38). Accuracy for automated processing was inspected by an expert (with 4 years of experience in editing data from more than 200 examinations and trained in this field) and manual corrections were applied if necessary.

We mapped these structures onto a spherical space to achieve point-to-point correspondence for each subject (39). The final segmentation of surface-based labeling was based on both a subject-independent probabilistic atlas and on subject-specific measured values. Combining the cortical-thickness map and surface-based labels, we computed the average cortical thickness for each region.

Statistical Analysis

The Shapiro–Wilk W-test was used to test for normality distribution of all continuous variables. The independent two-sample t-test and the Mann–Whitney test were used to compare group differences based on data normality, respectively. Chi-square analyses were applied to assess categorical variables. $P < 0.05$ were considered to indicate a significant difference. Effect sizes (Cohen's d) were computed to demonstrate the magnitude of observed differences. Two-sample t-tests were used to explore cortical thickness differences between groups from each native-surface region of interest (ROIs), and results were assessed for significance after controlling the false-discovery rate (FDR) at <0.05 to correct for multiple comparisons. The 2 × 2 (Group × Sex) mixed measures ANOVAs were performed to test the interactions and group effects, respectively. $P < 0.05$ were considered to indicate a significant difference. Simple effect was restricted to the ROIs showing significant interaction effect of group and sex. All regional results were Bonferroni-corrected by a factor of number of ROIs (N) showing significant interaction effect, corresponding to a corrected α of $P < 0.05/N$ after controlling for age and education level. Spearman's correlations were conducted between clinical assessments and the region-of-interest variables, since the data were not normally distributed.

RESULTS

Demographic and Clinical Characteristics

Thirty-seven patients with mTBI participated in this study. Of which, data from five patients were excluded because of poor MR imaging quality ($n = 3$), and excessive head motions ($n = 2$). Finally, 32 patients (18 male) were included. Thirty matched healthy controls (14 male) were also recruited. No significant difference was showed between patients with mTBI and healthy controls regarding age and education level. The average age was 33.4 years (range 14–54 years) in healthy controls, and was 31.0 years (range 13–59 years) in patients with mTBI [$F_{(1,60)} = 0.62$, $P = 0.43$, Cohen' s $d = -0.20$]. The average education level was 11.8 years (range 1–18 years) in healthy controls, and was 9.6 years (range 1–16 years) in patients with mTBI [$F_{(1,60)} = 2.88$, $P = 0.1$, Cohen' s $d = -0.43$]. No significant difference was in sex ($\chi^2 = 0.57$, $P = 0.45$). No significant difference was found in age and education level among the four groups (i.e., male and female controls and male and female patients with mTBI) [for age: $F_{(3,58)} = 1.98$, $P = 0.13$; for education level: $F_{(3,58)} = 1.32$, $P = 0.27$]. A detailed demographic data and clinical characteristics were summarized in the **Tables 1**, **2**. The major mechanism of trauma was a motor vehicle accident (11 of 18 male patients [61%], 10 of 14 female patients [71%]), followed by an assault (two of 18 male patients [11%], two of 14 female patients [14%]) ($P = 0.4$).

ANCOVAs (Group × Sex) analysis on the clinical assessments were conducted. The interaction effect of the group × sex was significant for the PCL-C [$F_{(1,58)} = 5.99$, $P = 0.017$] with simple effect testing suggested that females presented more complaints in the PCL-C compared with male counterparts only in the patient group but not in the control group ($P = 0.001$ after Bonferroni-correction) (**Table 2**). For patients, more complaints on the PCL-C was presented in both female ($P < 0.001$) and male ($P = 0.012$) compared with their corresponding controls.

Cortical Thickness Results

Patients with mTBI presented prominently reduced cortical thickness than healthy controls in the left entorhinal cortex, while significantly increased cortical thickness in the left precuneus cortex and right lateral occipital cortex ($P < 0.05$, FDR corrected, **Figure 1**). The interaction effect of the group × sex on cortical thickness was significant in the left caudal anterior cingulate cortex (caudal ACC) [$F_{(1,57)} = 5.976$, $P = 0.018$], fusiform cortex [$F_{(1,57)} = 10.13$, $P = 0.002$], insula cortex [$F_{(1,57)} = 7.35$, $P = 0.009$] and superior frontal cortex (SFC) [$F_{(1,57)} = 5.131$, $P = 0.027$] (**Figure 2**). Simple effect testing indicated that female patients had significant increased cortical thickness than male patients in the left caudal ACC ($P = 0.004$). Increased cortical thickness in the left SFC and fusiform cortex (all for $P = 0.005$) were also presented in female controls compared with male controls. Female patients had non-significant tendency of increased cortical thickness than male patients in the insula cortex ($P = 0.036$). Other comparison did not obtain the significance.

TABLE 1 | Demographic and Clinical assessments in patients of mTBI and healthy controls.

	Patients of mTBI				Healthy control subjects			
Demographic characterstics	**Female (*n* = 14)**	**Male (*n* = 18)**	***P***	**Cohen's d**	**Female (*n* = 16)**	**Male (*n* = 14)**	***P***	**Cohen's d**
Age	33.1 ± 14.3 (13∼59)	29.3 ± 10.3 (16∼48)	0.41	0.3	37.5 ± 12.3 (20∼54)	28.6 ± 8.4 (14∼53)	0.19	0.8
Education level	9.5 ± 4.5 (1∼16)	9.7 ± 3.2 (5∼15)	0.87	0.05	10.7 ± 4.7 (3∼18)	12.4 ± 4.8 (1∼18)	0.34	0.4
MECHANISM OF INJURY								
Motor vehicle accident	10 (71.4%)	11 (61.1%)						
Assault	2 (14.2%)	2 (11.1%)						
Fall	1 (7%)	2 (11.1%)						
Other	1 (7%)	3 (16.7%)						
CLINICAL ASSESSMENTS								
Trail making test A	55.1 ± 34.9	47.6 ± 22.5	0.712	0.3	49.4 ± 24.1	32.8 ± 22.4	0.093	0.7
RPCS	13.9 ± 8.7	6.9 ± 6.0	0.001	0.9	2.8 ± 2.8	1.1 ± 1.9	0.391	0.7
PCL-C	26.4 ± 8.6	21.0 ± 2.9	0.001	0.8	17.0 ± 0.0	17.0 ±0.0	1.000	Non
DSC	37.4 ± 17.0	35.2 ± 14.3	0.685	0.1	42.8 ± 17.0	54.7 ± 11.8	0.035	−0.8
Forward DS	8.2 ± 1.9	8.0 ± 1.5	0.705	0.1	7.7 ± 1.7	9.1 ± 1.1	0.020	−0.9
Backward DS	3.6 ± 1.7	4.3 ± 1.8	0.247	−0.39	3.8 ± 0.9	5.7 ± 2.0	0.002	−1.3
VF	17.2 ± 5.0	17.1 ± 6.0	0.931	0.01	17.2 ± 5.7	21.3 ± 5.7	0.052	−0.7

RPCS, Rivermead Post-Concussion Symptom Questionnaire; PCL-C, Posttraumatic stress disorder Checklist—Civilian Version; DSC, Digit Symbol coding; DS, Digit Span; VF, Verbal Fluency. Effect sizes reported are Cohen's d-values.

TABLE 2 | Demographic and Clinical assessments in female participants and male participants.

	Female participants				Male participants			
Characteristic	**MTBI patients**	**Healthy control**	***P***	**Cohen's d**	**MTBI patients**	**Healthy control**	***P***	**Cohen's d**
Age	33.1 ± 14.3 (13∼59)	37.5 ± 12.3 (20∼54)	0.18	−0.3	29.3 ± 10.3 (16∼48)	28.6 ± 8.4 (14∼53)	0.93	0.07
Education level	9.5 ± 4.5 (1∼16)	10.7 ± 4.7 (3∼18)	0.49	−0.26	9.7 ± 3.2 (5∼15)	12.4 ± 4.8 (1∼18)	0.07	−0.7
CLINICAL ASSESSMENTS								
TMT-A	55.1 ± 34.9	49.4 ± 24.1	0.862	0.2	47.6 ± 22.5	32.8 ± 22.4	0.124	0.7
RPCS	13.9 ± 8.7	2.8 ± 2.8	0.000	1.7	6.9 ± 6.0	1.1 ± 1.9	0.004	1.3
PCL-C	26.4 ± 8.6	17.0 ± 0.0	0.000	1.5	21.0 ± 2.9	17.0 ± 0.0	0.012	1.9
DSC	37.4 ± 17.0	42.8 ± 17.0	0.342	−0.3	35.2 ± 14.3	54.7 ± 11.8	0.001	−1.5
Forward DS	8.2 ± 1.9	7.7 ± 1.7	0.366	0.3’	8.0 ± 1.5	9.1 ± 1.1	0.062	−0.8
Backward DS	3.6 ± 1.7	3.8 ± 0.9	0.860	−0.1	4.3 ± 1.8	5.7 ± 2.0	0.023	−0.7
VF	17.3 ± 5.0	17.2 ± 5.7	0.962	0.01	17.1 ± 6.0	21.3 ± 5.7	0.042	−0.7

TMT-A, Trail making test A; RPCS, Rivermead Post-Concussion Symptom Questionnaire; PCL-C, Posttraumatic stress disorder Checklist—Civilian Version; DSC, Digit Symbol coding; DS, Digit Span; VF, Verbal Fluency. Effect sizes reported are Cohen's d-values.

Correlation Analysis Results

Spearman correlation analysis was only restricted into clinical assessment (PCL-C) and regional cortical variable showing a significant interaction effect. There was a significantly positive correlations between the cortical thickness of the left caudal ACC and PCL-C ratings only in female patients ($r = 0.594$, $P = 0.011$). No other correlation was presented in either female, male patients or whole patient group.

DISCUSSION

To our knowledge, this is the first study to examine sex differences in cortical thickness during the very early acute post-injury of mTBI. The present study indicated a salient modulatory effect of sex on both self-reported symptomatology (PCL-C) and regional cortical thickness following acute mTBI. Female patients had significant increased cortical thickness than male patients in the left caudal ACC. The increased cortical thickness in the

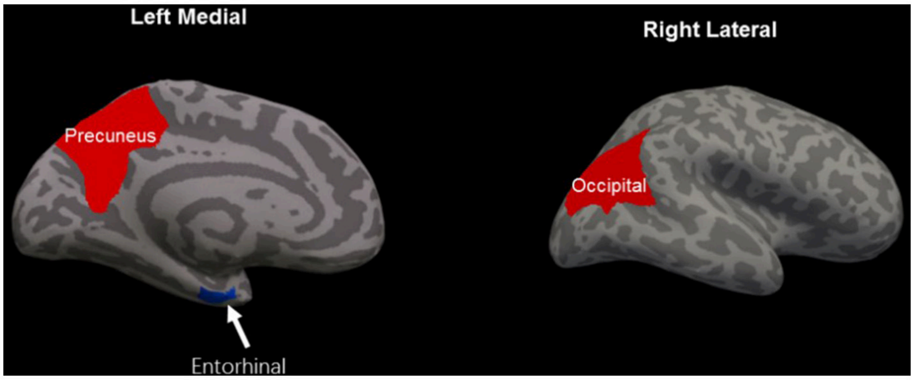

FIGURE 1 | Regions of significant cortical thinning (blue) and thickening (red) in mild traumatic brain injury patients, compared with healthy controls. Regions in the left entorhinal cortex, left precuneus cortex, and right lateral occipital cortex were significant at $P < 0.05$ after FDR correction.

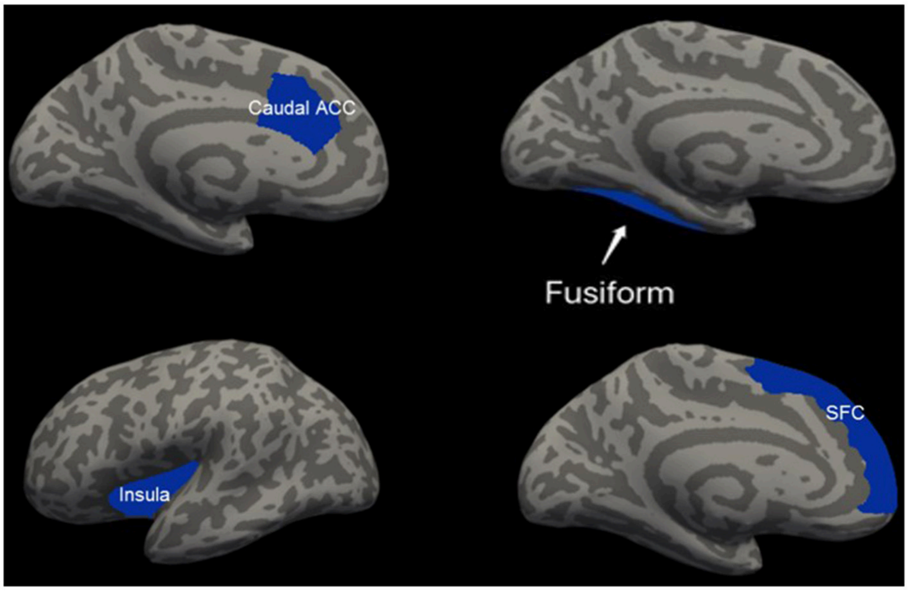

FIGURE 2 | Regions of significant increased cortical thickness (blue) in female participants, compared with male participants. Left column represents in patients with mTBI and right column represents in healthy controls. Regions in the caudal anterior cingulate cortex (caudal ACC), fusiform cortex and superior frontal cortex (SFC) in the left hemisphere were significant at $P < 0.0125$ after Bonferroni-correction. Region in the left insula cortex was not significant at $P = 0.036$ after Bonferroni-correction.

left caudal ACC was positively related with more complaints in the PCL-C ratings only in female patients. These findings may provide the clue to the management strategies for mTBI patients of different sexes.

Previous studies about sex differences in outcomes of mTBI revealed confounded results (4–6, 11, 13). A prior research suggested that it may be easier to admit their concussion symptoms after TBI for female athletes than male (12). Similarly, male concussion athletes presented more difficult to have a willing to report their symptoms than female athletes because of social norms (40) and the pressure to return to sports (41). Outcome differences in patients with mTBI could be masked by the subjective assessments. Our study avoids it by evaluating an objective measurement of the underlying neuroimaging detected injury using brain cortical thickness. To date, sex differences in cortical thickness have been reported in healthy individuals in several researches though no such findings were reported in mTBI (41). We found that the female healthy controls had significant increased cortical thickness than male controls in the left fusiform cortex, while this difference disappears modulated by the mild TBI (42). In addition, interaction effect of group and sex in the cortical thickness were primarily located in the four regions, including the left caudal ACC, fusiform cortex, insula cortex, and SFC. Based on these findings, sex difference in cortical thickness may be modulated by the injury.

We observed that the cortical thickness of female patients in the left caudal anterior cingulate cortex was positively related with the PCL-C scores. Previous work has shown that caudal anterior cingulate cortex is involved in motor control (43). For instance, it was reported that post-traumatic stress disorder (PTSD) is an anxiety disorder associated with the anterior cingulate cortex (ACC) (44). Results exhibited that decreased functional connectivity was observed between the caudal ACC and the precentral gyrus in veterans with PTSD compared to healthy controls. So we supposed that the thickened cortical thickness in left caudal anterior cingulate cortex may affect functional connectivity in female survivors. This possibility needs to be tested by future study to focus on dynamic structural and functional changes after mTBI. We have also found non-significant trend of thicker thickness in the left insula in the female patients, compared with male patients. Simple effect testing suggested that female patients had significant increased cortical thickness in this region than female controls that didn't found in the male groups ($P = 0.016$) after Bonferroni-correction. Such finding may be limited by the relatively small sample sizes. So we still speculated that it may due to the significant increased cortical thickness in female patients than male patients, compared with respective controls.

We did not explore the mechanisms that may contribute to cortical thickening in the current study, but several possibilities in this context can be considered. In animal studies, regional micro-edema has been found in thickened cortical regions within a day after cortical impact (45). Gray matter changes were in the form of increased, not decreased cortical thickness, which may have resulted from neuroinflammatory or other trophic process related to endocrine changes or functional compensation (46). Acute cerebral inflammatory reactions have been found to recover within months after injury and animal studies revealed thickened cortical regions became thinning over days with reduction of micro-edema (45). Unfortunately, we still need to conform such changes in cortical thickness after mTBI in a more chronical follow-up.

There are several limitations to our study. Post-injury time may be not long enough to observe cortical changing at acute phase and longitudinal analysis needs to be involved using following-up data. Furthermore, we did not evaluate the heterogeneity of injury, future studies should use additional outcome measures, including diffusion tensor imaging for structure integrity, resting state functional connectivity study for dynamic changes in functional networks, perfusion of cerebral blood flow (CBF) for brain metabolism using Arterial Spin Labeling Technology (ASL), which may be helpful in understanding the underlying pathophysiology and causes of sex differences in mTBI. Considering the selection of control may influence the detected injury pattern following mTBI, further study needs to enroll both orthopedically-injured patients and healthy subjects as different control group for comparison.

CONCLUSIONS

In conclusion, the study presented the abnormal cortical thickness changes related to sex in patients with mTBI, which correlated with the more possibility to develop PTSD and impairments in the information processing speed. Thus, our results indicated a role for cortical thickness as a metric for evaluating the sex difference of mTBI injuries and may predicting subsequent clinical outcome.

AUTHOR CONTRIBUTIONS

MS, LB, ZY, BY, and GB contributed to the conception of the study. MS, JC, and LB contributed significantly to analysis and manuscript preparation. MS, JC, LB, and SW performed the data analyses and wrote the manuscript. WH, SW, CS, SG, LY, DZ, CG, and LH helped perform the analysis with constructive discussions.

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Employment Probability Trajectories Up To 10 Years After Moderate-To-Severe Traumatic Brain Injury

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Aims: To examine trajectories of employment probability up to 10 years following moderate-to-severe traumatic brain injury (TBI) and identify significant predictors from baseline socio-demographic and injury characteristics.

Methods: A longitudinal observational study followed 97 individuals with moderate-to-severe TBI for their employment status up to 10 years post injury. Participants were enrolled at the Trauma Referral Center in South-Eastern Norway between 2005 and 2007. Socio-demographic and injury characteristics were recorded at baseline. Employment outcomes were assessed at 1, 2, 5, and 10 years. Hierarchical linear modeling (HLM) was used to examine employment status over time and assess the predictors of time, gender, age, relationship status, education, employment pre-injury, occupation, cause of injury, acute Glasgow Coma Scale (GCS) score, duration of post-traumatic amnesia (PTA), CT findings, and injury severity score, as well as the interaction terms between significant predictors and time.

Results: The linear trajectory of employment probabilities for the full sample remained at ∼50% across 1, 2, 5, and 10-years post-injury. Gender ($p = 0.016$), relationship status ($p = 0.002$), employment ($p < 0.001$) and occupational status at injury ($p = 0.005$), and GCS ($p = 0.006$) yielded statistically significant effects on employment probability trajectories. Male gender, those in a partnered relationship at the time of injury, individuals who had been employed at the time of injury, those in a white-collar profession, and participants with a higher acute GCS score had significantly higher overall employment probability trajectories across the four time points. The time*gender interaction term was statistically significant ($p = 0.002$), suggesting that employment probabilities remained fairly stable over time for men, but showed a downward trend for women. The time*employment at injury interaction term was statistically significant ($p = 0.003$), suggesting that employment probabilities were fairly level over time for those who were employed at injury, but showed an upward trend over time for those who had been unemployed at injury.

Conclusion: Overall employment probability trajectories remained relatively stable between 1 and 10 years. Baseline socio-demographic and injury characteristics were predictive of employment trajectories. Regular follow-up is recommended for patients at risk of long-term unemployment.

Keywords: brain injury, outcome assessment, prospective studies, return to work, rehabilitation

INTRODUCTION

The majority of individuals with traumatic brain injuries (TBIs) in high-income countries survive due to improvements in overall trauma care (1). Most survivors are of working age (2), and one of the challenges for this group is to return to work and maintain employment over time (3–6). The participation in employment represents a key rehabilitation goal after TBI in order to avoid the personal and socio-economic burden of unemployment. Identifying early prognostic factors associated with employment and employment probability trajectories can help identify persons who are at risk of unemployment and to alleviate the burden of TBI through more effective vocational rehabilitation programs.

Despite substantial research regarding employment outcomes and their prognostic factors (7–13), there are few studies looking at employment probability from a long-term perspective after TBI (i.e., 10 years after injury) (14). Ponsford et al. (15) examined aspects of functioning affected by complicated mild to severe TBI over a span of 10 years and found that only half of the sample returned to previous leisure activities and fewer than half were employed at each follow-up post-injury (2, 5, and 10 years). More recently, Cuthbert et al. (16) studied the 10 years patterns of employment in working age persons with moderate-to-severe TBIs who were discharged from a Traumatic Brain Injury Model Systems (TBIMS) center in the United States. They used a generalized linear mixed model, and included 1, 2, 5, and 10 years follow-ups. Results indicated that age, gender, cultural factors, education, duration of post-traumatic amnesia (PTA), and pre-injury substance abuse significantly predicted the trajectory of post-injury employment. The authors concluded that the overall decline in trajectories of employment probability between 5 and 10 years post-injury may suggest the chronic effects of TBI, and the influence of national and labor market forces on employment outcome. Similarly, Grauwmeijer et al. (14) evaluated the predictors and probability of employment over a 10 years period (3, 6, 12, 18, 24, and 36 months and 10 years post-TBI) in a Dutch sample of moderate-to-severe TBIs using generalized estimating equations and a logistic regression analysis. The authors concluded that 10 years employment probability is related to time, severity of injury and pre-injury employment. After an initial increase in the first 2 years post TBI, the employment probability stabilized at 57% after 2 years and decreased to 43% in the long-term (14), in line with the study by Cuthbert et al. (16).

Taken together, in addition to the socio-demographics and injury related characteristics, differences in governmental policies, health care and welfare systems, rehabilitation services, and culture may influence the predictors of employment trajectories (5, 13, 16–19). Thus, studies from different countries are required to provide a better understanding of factors influencing the employment probability and needs of rehabilitation and long-term follow-up programs.

We previously reported the employment probability trajectories up to 5 years post-injury (5) by using multi-level modeling, and found fairly constant employment rates of ∼50% across the three follow-up time points at 1, 2, and 5 years post-TBI. Being single, unemployment at the time of injury, blue collar occupation, lower GCS score at hospital admission, and longer duration of PTA were significant predictors of unemployment at 1, 2, and 5 years post-injury.

This study is an extension which aims to examine employment probability trajectories up to 10 years after moderate-to-severe TBI, and to investigate whether those trajectories could be predicted by socio-demographics and injury characteristics. Based on the previously mentioned studies from the US and Netherlands, we hypothesized that the employment probability would decrease from 5 to 10 years post-injury.

MATERIALS AND METHODS

Participants

A longitudinal cohort study was conducted including patients with acute TBI who had been admitted from 2005 to 2007 to the Trauma Referral Centre for the South-Eastern region of Norway, covering a population of nearly 2.6 million people. Patients were assessed in the acute phase (baseline) and followed up at 1, 2, 5, and 10 years after injury. Inclusion criteria were (a) age 16–55 years, (b) residence in eastern Norway, (c) admission with ICD-10 diagnosis S06.0–S06.9 within 24 h of injury, and (d) presence of moderate-to-severe TBI with a Glasgow Coma Scale (GCS) (20) score of 3–12 at admission or before intubation. Exclusion criteria were (a) previous neurological disorders/injuries, (b) associated spinal cord injuries, (c) previously diagnosed severe psychiatric or substance abuse disorders, and (d) unknown address or incarceration. For additional details, see study by Forslund et al. (5).

Overall, 133 individuals met the inclusion criteria. Thirty-two patients died during the acute or post-acute phase and four withdrew, leaving 97 survivors analyzed in this study (see **Figure 1**). The overall attrition rate in the surviving population was 21%. Because full information maximum likelihood (FIML) estimation was used to account for missing data at the various follow-ups, all participants were able to be retained in the model, generating statistical estimates that were unbiased due to attrition.

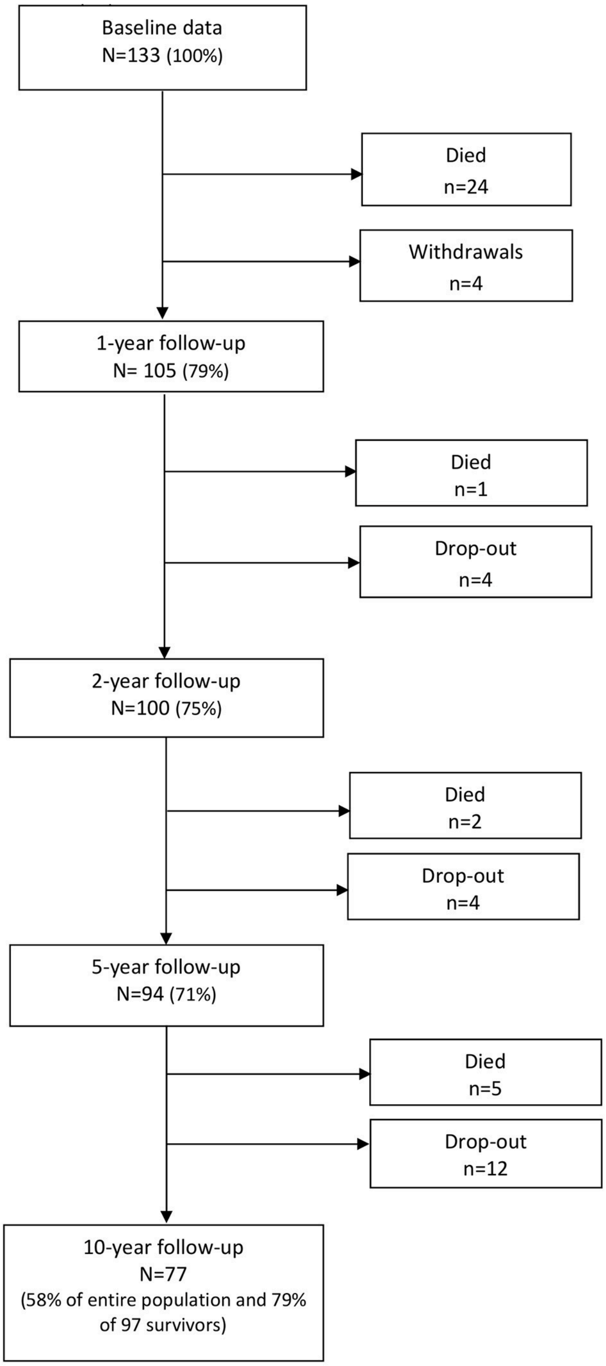

FIGURE 1 | Flowchart.

Measures

The outcome variable in this study was employment status at 1, 2, 5, and 10 years after injury. Employment was dichotomized into employed and unemployed, where individuals in the employed group consisted of individuals working full/part time or studying (high school, college, or university), while members of the unemployed group were jobseekers, on sick leave or work assessment allowance, or receiving disability pension. Working or studying full time was equal to 37.5 productive hours per week (i.e., 100% in Norway), while part-time employment was defined as working <37.5 h per week.

The independent variables (predictors) used in this study were: Gender (male vs. female), age at time of injury (in years), relationship status at hospital admission (partnered [married/cohabitant] vs. single), education (≤12 years vs. >12 years), employment status at time of injury (employed vs. unemployed), occupation prior to admission [blue collar (physical work) vs. white collar (non-physical work/being a student)], acute GCS (continuous), cause of injury (traffic accident vs. other), length of PTA (number of days) measured by the Galveston Orientation and Amnesia Test (GOAT) (21), Injury Severity Score [ISS; range from 1 to 75 (best to worst)] (22), and CT severity score. All patients had an acute CT head scan followed by a second control scan between 6 and 12 h after the injury. All CT scans were assessed and categorized by the same neuroradiologist according to the Marshall CT classification (23). The CT scan that showed the most extensive degree of intracranial damage (i.e., the largest hematoma thickness/midline shift and/or with the most extensive degree of parenchymal damage) within the first 24 h was used for classification.

Procedure

Pre-injury and injury-related characteristics from the acute phase were extracted from medical records. At the 1, 2, 5, and 10 years follow-ups, a physiatrist performed the assessments and interviews of patients at the outpatient department. Several patients made requests that the assessments and interviews should be conducted by telephone, and this was complied with. The study was approved by the Regional Committee for Medical Research Ethics, East Norway, and the Norwegian Data Inspectorate. All participants gave their written informed consent to participate in the study.

Data Analysis

Descriptive statistics were used to present demographics and injury related variables, and results are presented as percentages and means with standard deviations (SD) as appropriate. Hierarchical linear modeling (HLM) was used to examine trajectories of employment probability across 1, 2, 5, and 10 years after injury and identify baseline predictors. HLM was selected so that a full trajectory across all four time points could be analyzed and predicted, as opposed to separate and limited predictions of employment probability at each independent time point. A conditional (null) model was run first to determine whether there was sufficiently large clustering of employment probability variance within participants to proceed with HLM.

Unconditional growth linear (straight line), quadratic (U-shaped), and cubic models (S-shaped) were then run with no predictors to determine the most accurate model for linear or polynomial (curved) architecture of employment probabilities over time.

Once the most accurate curvature model was identified, predictors were entered simultaneously as fixed effects into an HLM after being centered or given a reference point of 0, along with time (given that linear trajectories of employment probabilities were found, outlined below). The HLM determined whether linear trajectories of employment probabilities across the four time points could be predicted by the demographic and injury characteristics of time [coded as 0 (1 year), 1 (2 years), 4 (5 years), or 9 (10 years) to reflect actual spacing between time points], gender (1 = female, 0 = male), age, relationship status (1 = partnered, 0 = single), education (1 = >12 years, 0 = ≤12 years), employment at admission (1 = employed, 0 = unemployed), occupational status (1 = white collar, 0 = blue collar), continuous GCS score, cause of injury (1 = motor vehicle, 0 = not motor vehicle), length of PTA (days), CT severity score, and ISS. A second HLM included the significant predictors identified from the full HLM, the variable of time, and interaction terms between the variable of time and the significant predictors.

RESULTS

The mean age of the 97 patients at the time of injury was 30.3 (SD = 10.8) years, 76% were men and 60% were injured in traffic accidents. The mean GCS at hospital admission was 7.2 (SD = 3.2). Of all patients, 73% received inpatient rehabilitation with mean length of stay 59 days (SD = 37 days). Demographics and injury-related characteristics are presented in **Table 1**.

Of all patients, 18% were unemployed at the time of injury (jobseekers 7%; work assessment allowance 5%; sick leave 2%; disability pension 4%). Of these, 80% were men, 60% >30 years, 70% with <12 years of education and 60% living alone.

The employment rate dropped from 82% pre-injury to 53% at 1 year follow-up and thereafter remained fairly stable up to 10 years (48, 55, and 50% at 2, 5, and 10 years follow-ups). At 10 years follow-up, 28% of the patients were in full-time jobs. Among the 22% of patients who were in part-time jobs, the majority (76%) received graded disability pension. Of the unemployed patients, 80% received full disability pension, 13% received work assessment allowance, and the remaining patients were jobseekers. A majority (79%) of the patients who were unemployed at 10 years were in the severe TBI group as measured by the GCS at injury time.

Unconditional Model and Unconditional Growth Models

The unconditional model yielded a statistically significant estimated participant variance of 0.17 (Wald Z = 6.05, $p < 0.001$), as well as a statistically significant estimated residual variance of 0.08 (Wald Z = 11.33, $p < 0.001$). The intraclass correlation coefficient was calculated to be 0.68, indicating that ∼68% of the total variance of employment probabilities was associated with the participant grouping (i.e., based on employment probability being correlated within each participant) and that the assumption of independence was violated. This suggests there was sufficiently large clustering of employment probability variance within participants to proceed with HLM. In other words, an intraclass correlation coefficient this high suggests a fairly high level to which employment probability is consistent across the same individual. The unconditional growth model was then run separately with the successive additions of time (-2LL = 321.50) quadratic time (-2LL = 321.35) and cubic time (-2LL = 315.48) in order to determine the shape of the best fitting architecture of employment probabilities over time, suggesting that a linear (straight line) trajectory best fit employment probability trajectories (The critical X^2 value for significant difference at $\alpha = 0.05$ is a >3.841 drop from the previous model).

TABLE 1 | Demographics at time of injury and injury characteristics.

Variable	*n* (%)	Mean (SD)	Total *n*
Age at injury in years		30.3 (10.8)	97
Gender			97
Male	76 (78.4)		
Female	21 (21.6)		
Relationship status			97
Partnered	28 (28.9)		
Single	69 (71.1)		
Education level			96*
≤12 years	54 (56.3)		
>12 years	42 (43.7)		
Employment status			97
Yes	80 (82.5)		
No	17 (17.5)		
Occupational status			97
Blue collar	46 (47.4)		
White collar	51 (52.6)		
Disability pension	4 (4.0)		
Injury cause			97
Traffic accident	58 (59.8)		
Other	39 (40.2)		
Glasgow Coma Scale (GCS)		7.2 (3.2)	97
Moderate (9–12)	32 (33.0)		
Severe (3–8)	65 (67.0)		
Post-traumatic amnesia (PTA) in days		26.0 (30.0)	91**
CT Head Marshall Score		2.6 (1.1)	97
Score 1–2	46 (47.4)		
Score 3+	51 (52.6)		
Injury Severity Score		30.0 (13.6)	97
Total acute length of stay in days		29.0 (25.0)	97
In-patient rehabilitation length of stay in days		59.0 (37.0)	71***

Missing data on 1 individual.

***Missing data on 6 individuals.*

****Only 71 individuals received in-patient rehabilitation (length of stay and mean stay is only calculated for those actually receiving it rather than the whole population).*

Full Model

An HLM examined whether employment probability trajectories over time could be predicted by socio-demographic and injury characteristics at the time of injury. All statistically significant and non-significant fixed effects from the full HLM and their b-weights, *p*-values, and 95% confidence intervals appear in **Table 2**. The linear trajectory of employment probabilities remained level over time across the full sample (e.g., no significant increase or decrease). Gender, relationship status at injury, employment at injury, occupational status, and GCS all yielded statistically significant effects on participants' employment probability trajectories.

Men had a higher overall employment probability trajectory across the four time points compared to women (**Figure 2**). Individuals who had been in a partner relationship at the time of injury had a slightly higher probability trajectory of employment than those who had been single, although this effect seemed to be driven by the first three time points (**Figure 3**). Individuals who had been employed at the time of injury had a higher probability trajectory of employment than those who had been unemployed at injury (**Figure 4**). Individuals in a white collar occupation had a higher probability trajectory of employment than those in a blue collar occupation (**Figure 5**). Finally, participants with a lower GCS score had a lower employment probability trajectory than those with a higher score (**Figure 6**).

Model With Time Interactions

An HLM examined whether employment probability trajectories could be predicted by the previously significant predictors (gender, relationship status at injury, employment at injury, occupational status, and continuous GCS), time, as well as their interactions with time (see **Table 3**). The time*gender interaction term was statistically significant ($p = 0.002$), suggesting that employment probabilities remained fairly stable over time for men but showed a downward trend over time for women (**Figure 2**). The time*employment at injury interaction term was statistically significant ($p = 0.003$), suggesting that employment probabilities were fairly level over time for those who had been employed at injury but showed an upward trend over time for those who had been unemployed at injury (**Figure 4**). The time*occupational status interaction term approached significance ($p = 0.069$) (**Figure 5**).

DISCUSSION

The present study is an extension of a study performed by Forslund et al. (5) which reported employment probability trajectories up to 5 years post-injury. This paper describes the 10-years trajectories and predictors of employment for 97 individuals with moderate and severe TBI.

Based on previous studies (14, 16), we hypothesized that the employment probability would decrease from 5 to 10 years post injury. Contrary to our hypothesis, the overall employment rates for the full sample remained relatively stable between 1 and 10 years at ∼50% (5). The baseline employment rates were comparable to employment rates in the general population aged 25–54 years (Statistics Norway). In the past 8 years, there has been a slight decline in the employment rates in Norway. It is not possible to deduct whether the return to work process in the study population were affected by the slight general decrease in employment rates. However, even though the number of patients receiving disability pension in our study increased across the follow-ups, the percentage of jobseekers remained unchanged when comparing the baseline assessment and 10 years follow-up data.

Dahm and Ponsford (24) investigated employment trajectories after complicated mild-to-severe TBI and found an employment rate of 58% at the 10 years follow-up. Ponsford et al. (15) reported that 40% returned to open employment in some capacity and that this percentage remained stable over the first 10 years after mild-to-severe TBI in Australia. A stable employment rate across the follow-ups is probably an expression of "plateauing" of recovery after the 1st year following the injury (14, 25), but may also indicate a lack of effective, individually customized vocational rehabilitation programs aiming to improve workability and return to employment (26) such as vocational rehabilitation with supported employment (3).

Compared to the study by Grauwmeijer et al. (14), we included younger patients (age at the time of injury 16–55 years vs. 16–67 years), which may positively influence the employment probability results. The study by Cuthbert (16) included patients in the same age range as ours; however, their patients were selected from inpatient rehabilitation centers, thus representing more severe injuries which may lead to persistent, chronic consequences, with late deterioration and more unfavorable long-term outcomes. Nonetheless, methodological differences and the influence of national welfare provisions and labor market forces make it difficult to compare the employment trajectory results across countries. We can only speculate whether the demographic and injury characteristics, changes in the labor market, and welfare system differences contribute to the stable employment rates found in this study.

The following predictors were statistically significant in the models used in this study: employment at injury, relationship status, occupational status, and GCS. This is in line with results from the 5 years follow-up (5) acknowledging the importance of these factors when predicting employment outcomes after TBI. The study results demonstrated that participants who had higher GCS scores at the time of injury, and were in white-collar occupations, had significantly higher probability of being employed at all time-points. Severity of TBI (i.e., GCS score) has consistently been linked to long-term employment outcomes (5, 27, 28). Although non-significant, there was a trend toward an association between duration of PTA and employment status at 10 years. This is in accordance with previous long-term studies (16, 24), and the 1, 2, and 5-year follow-up of the current sample (5). The association between having a blue-collar occupation (i.e., manual labor) at the time of injury and post-injury unemployment is consistent with a review by Ownsworth and McKenna (29) and a study by Walker et al. (30), showing support for the association between pre-injury occupational status and employment outcomes. Being in a partner relationship at time of injury was found to significantly

TABLE 2 | Demographic and injury predictors of employment probability trajectories across 1, 2, 5, and 10 years.

Predictor	*b*-weight	*SE*	*p*-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	0.018	0.109	0.870	−0.198	0.234
Time	−0.002	0.005	0.642	−0.012	0.008
Gender (1 = female, 0 = male)	−0.222*	0.090	0.016	−0.400	−0.043
Age	−0.006	0.004	0.159	−0.015	0.002
Relationship Status (1 = partnered, 0 = single)	0.305**	0.097	0.002	0.112	0.498
Education	−0.045	0.050	0.367	−0.143	0.054
Employment (1 = employed, 0 = unemployed)	0.447***	0.097	<0.001	0.254	0.640
Occupational Status (1 = white collar, 0 = blue collar)	0.243**	0.085	0.005	0.074	0.411
GCS	0.038**	0.014	0.006	0.011	0.065
Cause of Injury (1 = motor vehicle, 0 = not motor vehicle)	0.007	0.085	0.936	−0.161	0.175
PTA	−0.003	0.001	0.068	−0.006	0.000
CT Severity Score	−0.031	0.037	0.404	−0.104	0.042
ISS	−0.003	0.003	0.267	−0.009	0.003

** = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.*

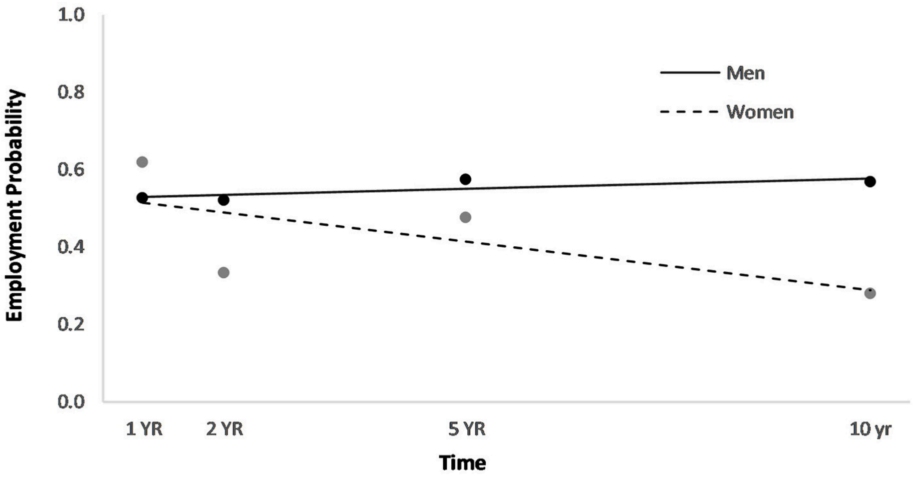

FIGURE 2 | Main effect of gender on employment probability trajectories.

improve employment probability trajectories in the present study (although the effect was driven by the first time points). The results are in line with previous studies (9, 17, 31) suggesting that marital/relationship status is a significant predictor of post-injury employment.

The finding that participants who were unemployed at the time of injury were significantly less likely to be employed at each of the four time points is consistent with previous literature (5, 10, 17). A possible explanation for this finding is that previous work experience, as well as familiarity with the workplace and specific tasks, may make the transition back to work more easily achievable for those who are employed at the time of injury. Interestingly, the time*employment at injury interaction term was significant, suggesting that those who had been unemployed at the time of injury had an increased likelihood of being employed at the 10 years follow-up. One of the reasons may be that the majority of patients in the unemployed group were job seekers or on work assessment allowance at the time of injury, thus having the prospect of attaining jobs over time. Different workfare programs have been introduced in Norway over the last decade to meet problems in the labor market. One of the programs is the Inclusive Working Life (IW) Agreement introduced by the Norwegian Labor and Welfare Service to create a more inclusive workplace through adaptation and improvement of the work environment, reducing the utilization of sick leave and disability benefits, and retaining senior employees longer (32). The IW Agreement covers approximately 60% of the country's employees (33). However, the IW agreement has been questioned due to implementation problems and whether challenges concerning sickness related welfare consumption need to be regarded in a wider context (32).

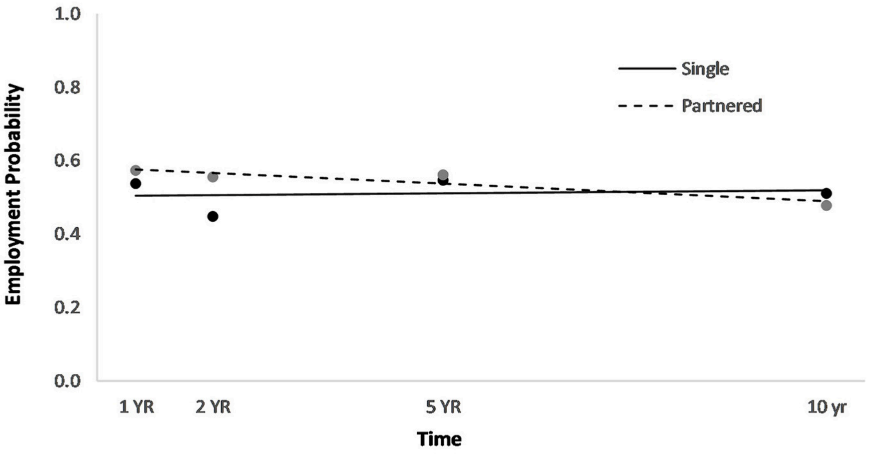

FIGURE 3 | Main effect of relationship status at injury on employment probability trajectories.

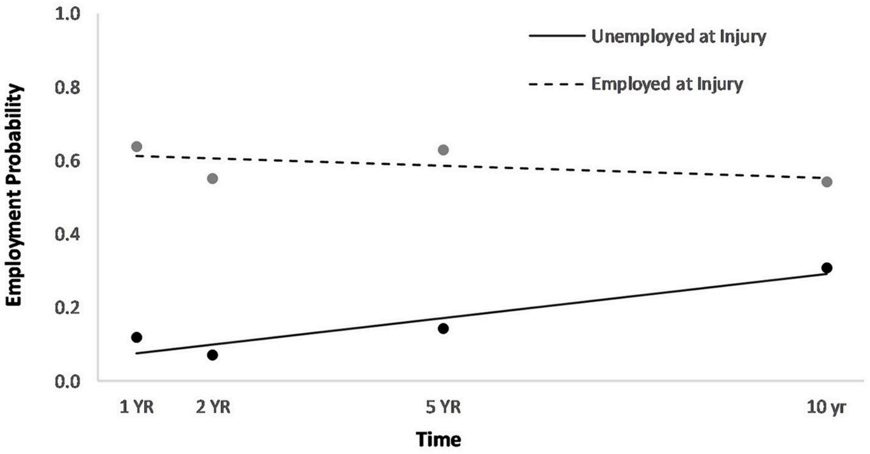

FIGURE 4 | Main effect of employment at injury on employment probability trajectories.

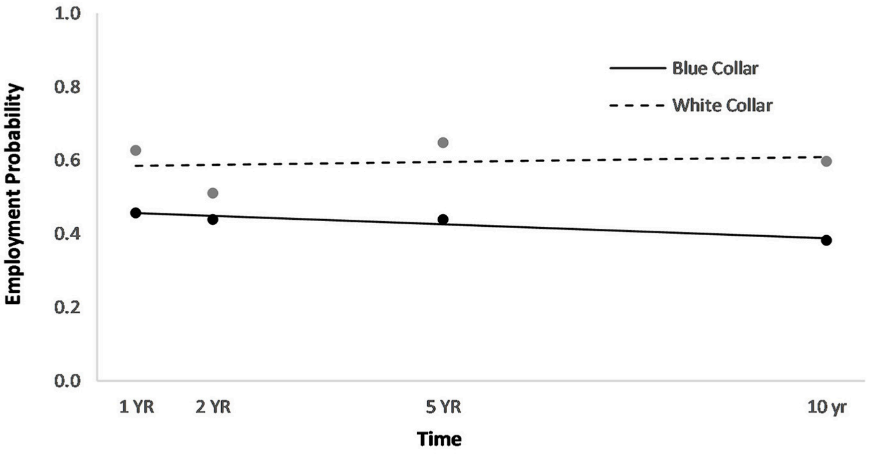

FIGURE 5 | Main effect of occupational status on employment probability trajectories.

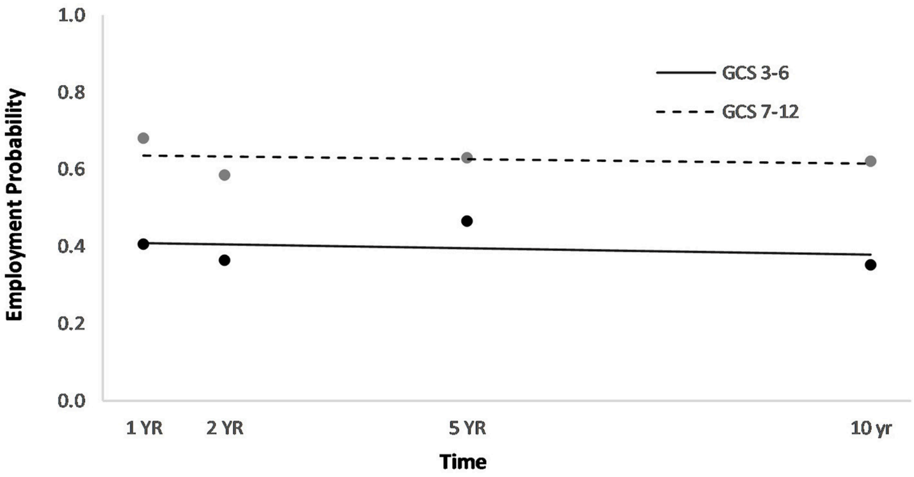

FIGURE 6 | Main effect of GCS (dichotomized at mean value) on employment probability trajectories.

TABLE 3 | Previously significant predictors and their time interaction effects on employment probability trajectories across 1, 2, 5, and 10 years.

Predictor	*b*-weight	*SE*	*p*-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	−0.007	0.102	0.947	−0.210	0.196
Time	0.026*	0.012	0.033	0.002	0.051
Gender (1 = female, 0 = male)	−0.069	0.098	0.478	−0.263	0.124
Relationship Status (1 = partnered, 0 = single)	0.090	0.093	0.334	−0.094	0.274
Employment (1 = employed, 0 = unemployed)	0.532***	0.106	<0.001	0.322	0.742
Occupational Status (1 = white collar, 0 = blue collar)	0.133	0.086	0.124	−0.037	0.304
GCS	0.061***	0.012	<0.001	0.036	0.085
Time*Gender	−0.034**	0.011	0.002	−0.056	−0.013
Time*Relationship Status	−0.003	0.010	0.754	−0.024	0.017
Time *Employment	−0.036**	0.012	0.003	−0.060	−0.012
Time*Occupational Status	0.018	0.010	0.069	−0.001	0.038
Time*GCS	−0.002	0.001	0.120	−0.005	0.001

** = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.*

Regarding gender differences in employment probability over time, a downward trend in employment for women was observed, while men's probabilities remained constant. The existing literature on this topic has shown mixed results (29). A study by Corrigan et al. (34) investigated changes in employment 1 year after TBI and found that women were more likely to decrease working hours or be unemployed compared to men. Fraser et al. (28) found that women were more likely than men to maintain complex work post-injury. In line with our findings, the more recent study by Cuthbert et al. (16) demonstrated a significant relationship between being female and decreased probability of employment, the same was reported in a systematic review by Willemse-Van Son (8). Possible explanations for gender-differences in employment outcome following TBI have ranged from societal influences related to gender roles, differences in job-demands, to biological differences (35). Nevertheless, there is a trend in the general population that women report more symptoms as compared to men, that there is higher percentage of women on sick leave, and that women more often have part-time jobs (36).

Limitations and Future Directions

The current study is an extension of an existing longitudinal TBI research project. Several limitations inherent in the original design need to be acknowledged when interpreting the results. Firstly, although the study population was unselected and representative of working-age patients with moderate-to-severe TBI from the South-Eastern region of Norway, the inclusion and exclusion criteria from the original study, particularly the patients' age range at the study admission (16–55 years) and geographic setting, may limit the generalizability of the findings to a broader patient population and other healthcare settings. Secondly, the definition of employment used in this study may be a source of bias, thus limiting generalizability. Employment was categorized into unemployed (jobseekers, on sick leave or work assessment allowance, or receiving disability pension), and employed (working full-time or part-time or studying), which may have been different from other studies. Thirdly, the overall sample size for the current study is relatively small. Future studies with a larger sample size are needed to verify the findings of this study, and to account for factors other than baseline characteristics (such as functional status) which we did not assess in this study. This includes several subjective and environmental factors that may influence the employment probability such as the ability to adapt, resilience, physical, emotional and social supports, as well as access to care and current vocational rehabilitation practice. The role of work-place related factors such as possibilities for adapted work tasks, work environment, features of work organization, and the role of management also needs to be investigated to a larger degree in future research, as most TBI studies rely exclusively of individual patient characteristics. More research is needed to clarify the association between gender and interaction effects between gender and other factors on employment following TBI. Despite these limitations, the results from this study provides important insight into trajectories and predictors of employment in the long-term perspective following TBI. This information may be useful for patients, clinicians, and employment authorities and underlines the need for regular follow-ups both short- and long-term. Given the individual and societal importance of employment and return to work after TBI, future research could examine employment in more granular terms. For instance, it would be interesting to understand how the type of work, adaptations at the work place, hours worked, and/or employment stability changes over time. This would require more frequent follow-up and collecting more detailed information regarding the survivor's job situation. Better knowledge of all these factors may encourage cross-sectoral collaboration between health care services and the labor and welfare system in order to develop new individualized work-related interventions to improve both short- and long-term employment outcomes.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Norwegian law on research ethics and medical Research, Regional Committees for Medical and Health Research Ethics of Norway with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Regional Committee for Medical Research Ethics, East Norway, and the Norwegian Data Inspectorate.

AUTHOR CONTRIBUTIONS

EH, NA, CR, SS, and MF contributed to study design, data acquisition, analysis, interpretation, drafting, and finalizing the manuscript. PP contributed to analysis, interpretation, drafting, and finalizing the manuscript. JA-L, JL, and ML contributed to data interpretation, drafting, and finalizing the manuscript.

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REVIEW
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A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury

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Mild traumatic brain injury (mTBI) presents a substantial burden to patients, families, and health care systems. Whereas, recovery can be expected in the majority of patients, a subset continues to report persisting somatic, cognitive, emotional, and/or behavioral problems, generally referred to as post-concussion syndrome (PCS). However, this term has been the subject of debate since the mechanisms underlying post-concussion symptoms and the role of pre- and post-injury-related factors are still poorly understood. We review current evidence and controversies concerning the use of the terms post-concussion symptoms vs. syndrome, its diagnosis, etiology, prevalence, assessment, and treatment in both adults and children. Prevalence rates of post-concussion symptoms vary between 11 and 82%, depending on diagnostic criteria, population and timing of assessment. Post-concussion symptoms are dependent on complex interactions between somatic, psychological, and social factors. Progress in understanding has been hampered by inconsistent classification and variable assessment procedures. There are substantial limitations in research to date, resulting in gaps in our understanding, leading to uncertainty regarding epidemiology, etiology, prognosis, and treatment. Future directions including the identification of potential mechanisms, new imaging techniques, comprehensive, multidisciplinary assessment and treatment options are discussed. Treatment of post-concussion symptoms is highly variable, and primarily directed at symptom relief, rather than at modifying the underlying pathology. Longitudinal studies applying standardized assessment strategies, diagnoses, and evidence-based interventions are required in adult and pediatric mTBI populations to optimize recovery and reduce the substantial socio-economic burden of post-concussion symptoms.

Keywords: mild traumatic brain injury, post-concussion symptoms, outcome, diagnosis, etiology, prevalence, treatment

INTRODUCTION

Mild traumatic brain injuries (mTBI) are among the most common neurologic conditions, representing a substantial burden in adults and children (1–3). A subset of mTBI patients suffers from acute **post-concussion symptoms** that may manifest as somatic symptoms (e.g., nausea, dizziness, headache, blurred vision, auditory disturbance, and fatigue), cognitive complaints (memory and executive function), emotional, and/or behavioral problems (e.g., disinhibition and emotional lability) (4–6).

In 10–25% of mTBI patients, post-concussion symptoms persist over time (7–10), which is often referred to as **post-concussion *syndrome* (PCS)**. PCS is usually diagnosed according to the International Classification of Diseases (ICD)-10 (5), or following Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (6). However, over the last 15 years the concept of PCS as a reliably identifiable, unique syndrome has been questioned (11, 12). Therefore, we will use the term post-concussion symptoms to describe symptoms following mTBI and will refer to *persistent* post-concussion symptoms when these persist for at least 3 months after TBI.

This focused review (based on a systematic literature search until March 1st 2018, see **Appendix A**) summarizes current knowledge on epidemiology, controversies, etiology, assessment and treatment of post-concussion symptoms in adults and children. Understanding the various factors leading to post-concussion symptoms, and the complex interactions between temporal onset, biological, psychological and social factors, as well as the relative influence of injury-related and non-injury related factors, may contribute toward a better understanding, diagnosis and classification of post-concussion symptoms. **Figure 1** shows current topics in research on post-concussion symptoms. In addition, an insight into the wide range of assessment methods and possible treatments may provide guidance for both clinicians (e.g., physician, psychologist, neuropsychologist, neurosurgeon, nurse, physical therapist, and occupational therapist), social worker and policy-makers.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We searched EMBASE and MEDLINE from Jan 1th, 2010 to March 1st 2018, where landmark papers with earlier dates were also integrated. We included papers published in peer-reviewed English language journals, identifying observational, experimental, and intervention studies and reviews in civilian mTBI patients with short- and long-term (3–36 m) post-concussion symptoms or syndrome. See **Appendix A** for the EMBASE search strategy. Additional papers were identified by screening reference lists and citation indices and from authors' own files.After removal of duplicates, articles were excluded on the basis of title and abstract by two reviewers (MC and DV).

To warrant a minimum level of quality, papers were selected for current review if they were either (systematic) reviews or prospective cohort studies that included $\geq$100 patients. Exceptions were imaging studies, where lower numbers of patients were allowed and studies about treatment, where we prioritized (randomized) controlled trials. If these studies were not available, we used either retrospective or case-control studies, studies with lower number of patients or papers published before 2010. In cases where included papers did not meet our quality threshold [review, prospective cohort $\geq$100 patients or randomized controlled trials (RCT)], this was explicitly mentioned.

DEFINITIONS AND EPIDEMIOLOGY

Mild Traumatic Brain Injury (mTBI)

The American Congress of Rehabilitation Medicine (ACRM) (4) defines mTBI as an "acute brain injury resulting from mechanical energy to the head from external physical forces," with any of the following symptoms: loss of consciousness (LOC) not exceeding 30 min, post-traumatic amnesia (PTA) of no more than 24 h, a score of no <13 on the Glasgow Coma Scale (GCS) after 30 min post injury (or upon presentation) (14), and an (unspecified) period of confusion (feeling dazed, disoriented, and confused), or other transient neurologic abnormalities such as focal signs or seizures.

Most mTBI patients do not show trauma-related abnormalities on computed tomography (CT) scans. However, the literature on mTBI frequently distinguishes between *complicated* and *uncomplicated* mTBI and the term *complicated mTBI* is often used to refer to e.g., 5–10% of emergency department (ED) patients (15) who show abnormalities, such as subarachnoid hemorrhage, intracranial contusions, or small extra-axial hematomas. The prevalence of pediatric mTBI based on emergency department visits are likely underestimated in childhood as studies have demonstrated that most children initially seek care with their primary care doctor for these mild injuries (16). In children, findings on CT are even more rare (17) and multiple effective clinical prediction rules have been developed to reduce unnecessary CT use in children (18). Special consideration should be given for children <2 years of age with regard to decision-making about the use of CT scans in the setting of head trauma.

Diagnosis of Post-concussion Syndrome

PCS is usually defined according to DSM-IV or ICD-10 criteria, which both focus on symptom presentation (19). These manuals agree on the prerequisite history of brain trauma for the diagnosis of post-concussional disorder [DSM-IV (6)] or PCS [ICD-10 (5)]. Differences between diagnostic systems are presented in **Table 1**. An important difference is that DSM-IV requires immediate symptom onset and persistence for at least 3 months whereas ICD-10 does not. In addition, DSM-IV requires objective evidence of memory or attention deficits (criterion B), but ICD-10 explicitly precludes such evidence (criterion C-3). The variability in terminology and associated criteria of the DSM-IV and ICD-10 hampers accurate identification and diagnosis of patients with PCS (13). Different classification methods may result in overestimation or underestimation of symptoms, particularly when relying on subjective endorsement of symptoms by patients. This was shown in a cross-sectional

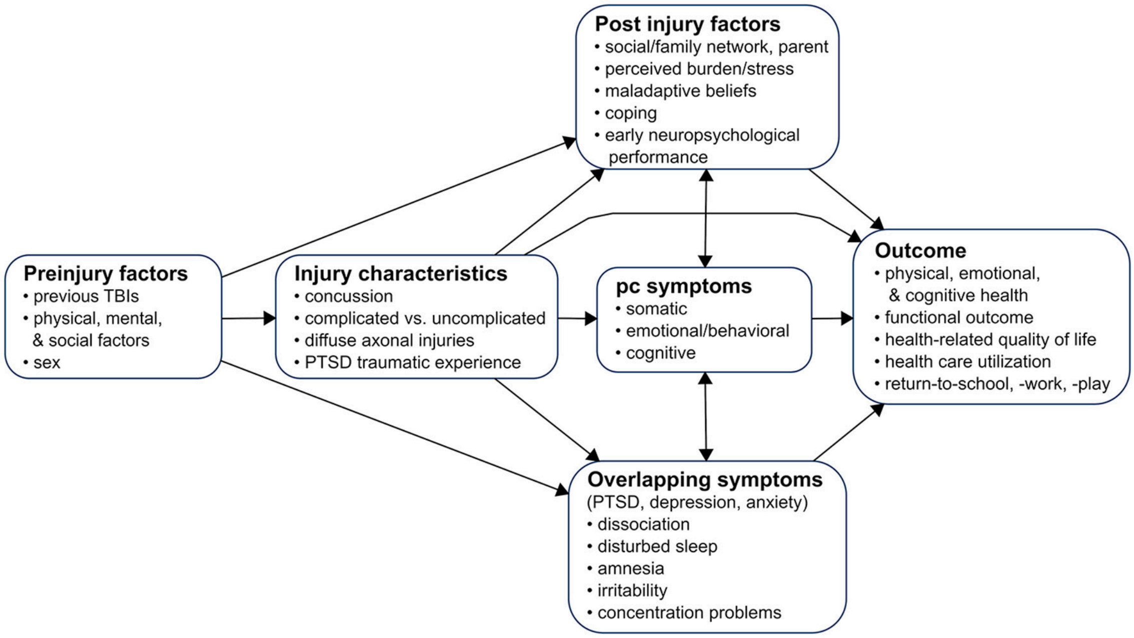

FIGURE 1 | A model for the study of post-concussion symptoms after mTBI. Permission has been obtained to model our figure based on Yeates (13), © The International Neuropsychological Society 2010, published by Cambridge University Press.

study in which 61 patients were referred to a concussion clinic following mTBI (20).

Post-concussional disorder was not included in the last DSM-5 edition (21). Instead, DSM-5 contains "mild neurocognitive disorder due to TBI," a neurocognitive disorder, which strongly suggests—but does not formally require—performance-based, quantifiable evidence of acquired cognitive deficits after mTBI (**Table 1**). Importantly, DSM-5 denotes the status of the most frequently reported post-concussion symptoms to the level of "associated features." Finally, DSM-5 emphasizes a broad range of differential diagnoses, especially when symptom severity "appears to be inconsistent with the severity of the TBI" (22).

Prevalence of Post-concussion Symptoms

Prevalence of post-concussion symptoms varies and depends on pre-injury factors (10, 23), patient population (24), assessment (24), and analytic strategies, diagnostic criteria (24, 25), and classification methods (26). Overall, single symptoms (e.g., fatigue, headache, and cognitive symptoms) are very common (27) (**Figure 2**), whereas multiple concurrent symptoms are less frequent (24).

Neuropsychological testing consistently shows minor cognitive deficits within the first 2 weeks after injury, with some exploratory evidence suggesting deficits lasting up to 6 months (28). It has been suggested that self-reported somatic symptoms (headaches, dizziness) are more prevalent immediately after the injury (1–2 weeks) (29), whereas cognitive and emotional symptoms resolve more slowly and may still be above baseline levels long-term post-injury (30, 31). However, these cross-sectional analyses did not track the evolution of symptoms in single patient groups. Therefore, evidence supporting a differential trajectory between self-reported somatic and cognitive/emotional subacute symptoms is limited.

ICD-10 prevalence rates of PCS at 3 months post-injury vary between 6% (32), 22% (33), and 64% (25). DSM-IV diagnostic criteria appear to be stricter than ICD-10 criteria leading to lower estimates (34): a cohort study of patients after mTBI found a prevalence of PCS at 3 months of 64% based on ICD-10 criteria, but only a prevalence of 11% when using DSM-IV (25).

Few pediatric studies report on the prevalence of post-concussion symptoms according to ICD-10 or DSM-IV diagnostic criteria; 1-month prevalence for children recruited from ED based on ICD-10 reach 52% (35) and 3-month prevalence based on DSM-IV constitutes 29.3% (36). Some studies define symptomatic children as having an increase in at least one symptom and arrive at estimates between 24.5 and 52.5% at 1 month post injury (35, 37), 11–39% after 3 months, and 2.3% at 12 months (35), which makes comparison of symptom development trends between children and adults challenging. An additional complication in capturing prevalence rates in children is that younger children may not be able to describe their symptoms reliably. Therefore, such prevalence estimates should be treated with caution.

CONTROVERSIES

Post-concussion symptoms are highly controversial and a major topic of debate among clinicians, methodologists, and health outcome experts. One problem is that post-concussion symptoms do not always cluster in a consistent and predictable manner (12,

TABLE 1 | Comparison of three definitions of post-concussion symptoms.

	ICD-10	DSM-IV	DSM-5
Headache	√	√	–
Dizziness	√	√	–
Fatigue	√	√	–
Noise intolerance	√	√	–
Irritability/lability/anxiety/ depression	√	√	–
Sleep problems	√	√	–
Concentration problems	√[A]	√[B]	√[B]
Memory deficit	√[A]	√[B]	√[B]
Intolerance of alcohol	√	–	–
Preoccupation with symptoms	√	–	–
Personality change	–	√	–
Apathy	–	√	–
Perceptual-motor	–	–	√[B]
Social cognition	–	–	√[B]

Table shows symptoms presented in the International Classification of Diseases (ICD)-10 definition of PCS (diagnosis code F07.02), the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV definition of postconcussional disorder and the DSM-V definition of neurocognitive disorder.

[A] *Subjective report.*

[B] *Objective test.*

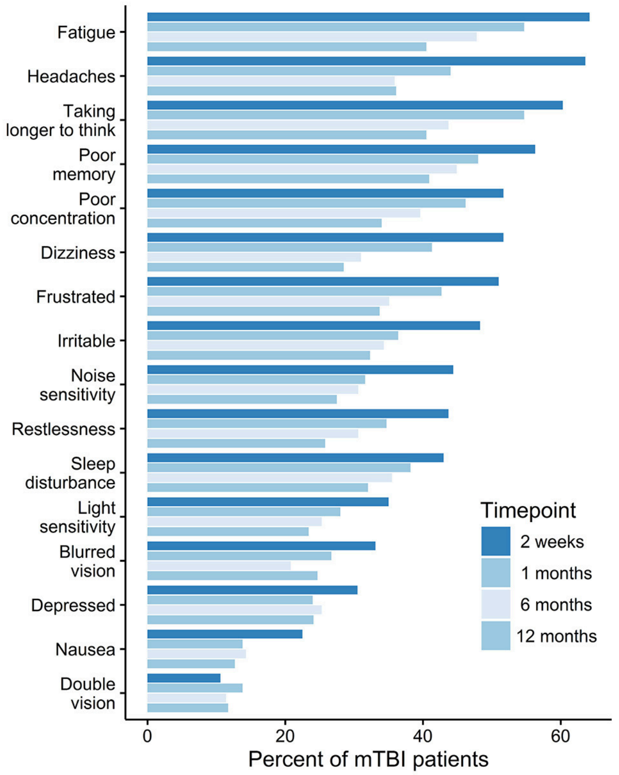

FIGURE 2 | The prevalence of post-concussion symptoms over time. *Permission has been obtained to base our figure on* data presented in Theadom (27).

19). Therefore, it is controversial whether they truly represent a specific, cohesive, and predictable syndrome (i.e., PCS) (12, 19). In addition, although the term post-concussion symptoms might suggest otherwise, these symptoms are not specific to TBI but are also frequently reported in non-brain injured trauma patients (10), including patients with whiplash injuries (38) and in healthy adults and children (35, 39, 40).

The literature on mTBI frequently uses the term "symptom" to refer to all changes experienced after a concussion. However, when focusing solely on the patient's self-report, the use of the term "complaint" might be more appropriate.

Similarly, the etiology of post-concussion symptoms is also debatable. Although the biopsychosocial model is often applied to explain the onset and persistence of post-concussion symptoms (41), post-concussion symptoms have also been associated with malingering, exaggeration, misattribution, and recall bias, thereby prompting concern regarding the clinical reality of post-concussion symptoms.

Acute and Persistent Post-concussion Symptoms

Acute post-injury symptoms, such as headache, dizziness, sensitivity to light or noise, double vision or tinnitus, are associated with the development of persistent symptoms (19, 42, 43). A clinical risk score in children has identified headache, sensitivity to noise, fatigue and answering questions slowly as predictive of post-concussion symptoms at 28 days post-injury (44). In addition, the experience of post-concussion symptoms early post-injury (1 week—1 month) is consistently associated with higher odds of persistent post-concussion symptoms (10, 45). A study from 2015 found that 82% out of 103 patients who were experiencing post-concussion symptoms 1 year after mTBI had already reported these 1 month post injury (46).

Biological Factors and Persistent Post-concussion Symptoms

Several, predominantly biological factors, such as diffuse axonal injury, neuro-inflammation, and altered cerebral blood flow have been implicated in the genesis of post-concussion symptoms after mTBI (41, 47, 48). However, these factors have not yet been analyzed in high-quality prognostic studies. The role of biological factors is supported by findings that repetitive mTBI is associated with increased symptom prevalence (49, 50), longer time to symptom resolution (50, 51), and a minimal effect of neurocognitive deficits (52). Similarly, repetitive sub-concussive impacts, e.g., in contact sports, have also been associated with minor long-term neuropsychological sequelae (53), abnormalities in both neuroimaging and in neuropsychological testing (54), and with the development of severe neurodegenerative conditions such as chronic traumatic encephalopathy (CTE) (54). Although many symptoms of CTE overlap with post-concussion symptoms (e.g., irritability, impulsivity, depression, (short-term) memory loss), current evidence on the association of repetitive sub-concussive impacts with CTE is limited and should be considered preliminary (55).

A major controversy in attempting to identify the role of biological factors in the development of post-concussion symptoms is their weak relationship with injury severity and the high prevalence of PCS-like symptoms in non-brain injured patients, as well as in healthy participants (10, 35, 37–40, 45, 56).

Even though most studies report that the rate of post-concussion symptoms is higher among brain-injured patients as compared to non-brain injured trauma controls (32, 46, 57–59), the high rate of false-positives needs to be taken into account when examining biological factors. It should be acknowledged that biological factors do not exist in isolation but need to be interpreted in the context of potentially confounding factors, e.g., pre- and post-injury physical and mental health, trauma, and psychosocial factors (10, 58–60).

Psychiatric, Psychological, (Psycho)-Social Factors and Post-concussion Symptoms

Psychiatric Factors

Many post-concussion symptoms (e.g., sleep difficulties, irritability and concentration problems) are similar to symptoms of the hyperarousal dimension of posttraumatic stress disorder (PTSD) (59), which may occur following exposure to severe, often life-threatening events. PTSD following mild, moderate, or severe TBI has a pooled prevalence rate of 13.8% (10.2–17.4%) (61) and appears to follow TBI more frequently than any other traumatic injuries not involving the brain (47, 62). Given the overlap between post-concussion and PTSD symptoms (59, 62, 63), careful differential diagnosis is required. Nevertheless, a prospective study including 534 brain-injured patients and 827 controls found that mTBI was a significant predictor for PTSD but not for post-concussion symptoms (59). It is not yet clear, whether these results also hold true for pediatric samples. A smaller prospective study comparing parent-reported post-concussion symptoms and PTSD symptoms in 186 children after mTBI and 99 children with non-head orthopedic injuries reported higher rates of post-concussion symptoms after mTBI but comparable rates of PTSD symptoms (63).

Almost half of patients with persistent post-concussion symptoms suffer from premorbid depression and anxiety (47, 64). Pre-injury mental health status has repeatedly been shown to predict persistent post-concussion symptoms in adult (41, 45, 47, 65) and pediatric populations (13, 35). However, the question of causality remains unclear, as psychiatric symptoms might be a reaction to experiencing persistent post-concussion symptoms, and/or mental health problems might increase the risk of reporting persisting symptoms.

Psychological Factors

Recall biases have been shown to influence reports of post-concussion symptoms after mTBI. Patients after mTBI expecting to experience post-concussion symptoms show higher symptom rates than patients not expecting to experience post-concussion symptoms (66). Similarly, in some patients the "good-old-days" bias may lead them to underestimate pre-injury symptoms (41, 57). If gross overrepresentation of symptoms is suspected (malingering), performance in selected neuropsychological tests can indicate whether the patient is exerting optimal effort (11, 67).

Finally, symptoms commonly occurring in everyday life, such as headache, irritability, sleep disturbance and forgetfulness may be misattributed to brain trauma (11, 33). Extensive assessments for putative somatic origins of such common symptoms may further make one believe that these symptoms are indicative of serious brain damage, leading to hypervigilance and catastrophic attributions, comparable to behaviors seen in patients with somatoform disorders or hypochondriasis (11, 33, 62, 67, 68).

Socio-Demographic, Social, and Personality Factors

Female sex is consistently associated with greater reporting of persistent post-concussion symptoms (45). Gender effects appear to be smaller in children (35, 37, 56). Some studies found that post-concussion symptoms are associated with lower education in adults (45) and pre-injury learning difficulties in children (37). Community integration, social support, lifestyle, and family dynamics may contribute to the development and persistence of post-concussion symptoms in adults (41, 69), and children (13, 70). However, conclusive evidence has not yet been established.

The five-factor model of Widiger and colleagues is a model of basic personality traits, consisting of five domains: neuroticism, extraversion, openness, agreeableness, and conscientiousness (71). Basic personality traits as captured in the five-factor model do not appear to be associated with persistent post-concussion symptoms (10). However, more specific traits such as high anxiety sensitivity (72), low resilience (73), coping styles (33, 74) or alexithymia (72) may be associated with persistence of symptoms. However, the cross-sectional design and small sample sizes in these studies hamper the establishment of firm conclusions in the area.

Predicting Persistent Post-concussion Symptoms

The identification of risk factors might be especially useful for clinical practice when combined into a prognostic model predicting patients at risk of poor outcome. However, current models are often based on small samples (9, 75) and lack internal and external validation (10, 45, 75, 76). In addition, no model is able to reliably predict outcomes at the individual patient level (45). Therefore, identification of high-risk patients might best be accomplished by careful and dense follow-up data collection. Advances in study and modeling methodology and, possibly, the incorporation of advanced imaging, and biochemical biomarkers (see **Panel 1** for recommendations) may improve the ability to identify at-risk patients in the first week post-injury in the future.

CLINICAL ASSESSMENT OF POST-CONCUSSION SYMPTOMS

Providing optimal care depends on early and reliable identification of patients at risk of developing persistent post-concussion symptoms (12, 80) by a multidisciplinary team. Medical examination should include a history of previous TBIs, head and neck injuries, and a detailed description of the number and extent of acute concussion symptoms, preferably using standardized instruments (see **Table 2**). Special emphasis

PANEL 1 | Methodological recommendations for studies on post-concussion symptoms after mTBI.

Well-designed confirmatory studies with the following characteristics have been called for to better understand post-concussion symptoms and its consequences:

- **Study design**: Prospective inception cohort studies with appropriate control group (e.g. non-brain injured patients, general population) and appropriate follow-up period to differentiate persistent deficits and symptoms due to post-concussion symptoms from the effects of pre-injury (neuro)psychiatric disorders and other non-mTBI factors. Longitudinal analyses strategies to monitor evolution of post-concussion symptoms in single patients.
- **Instruments**: use crosswalk analysis to compare incidence rates between studies using different post-concussion symptom assessment procedures. At a minimum, aim to include at least some comparable items, i.e., items whose functioning is comparable between patient samples, and evaluate other items relative to these anchor items. **Studies on predictors/prediction models** (based on Mushkudiani et al. (77) and Steyerberg (78):
    - ○ Sample size: N > 500
    - ○ Predictors should be based on theory, clinical knowledge or previous research
    - ○ For every predictor considered there should be at least ten cases (i.e., patients classified as having PCS)
    - ○ A liberal *p*-value (e.g., $p < 0{\cdot}157$) (79) should be used when applying selection procedures
    - ○ Results should be internally validated (e.g., bootstrap validation)
    - ○ Both discrimination and calibration statistics should be mentioned; a score chart is warranted for implementation in clinical practice
    - ○ External validation: external validation in an independent dataset is a prerequisite before implementation in clinical practice. External validation and updating of an existing model should be prioritized against the development of a new model.

should also be placed on the assessment of co-morbid injuries and disorders, such as chronic headache, and other pain, cervical-disorders, visual or vestibular disorders, chronic fatigue, sleep, and somatoform disorders (35, 65, 80, 81). However, checklists alone are not sufficient to provide a *diagnosis* of persistent post-concussion symptoms as a disorder in the absence of a comprehensive multidimensional medical, neurological, and psychiatric and (neuro)psychological evaluation (64, 82).

Since persistence of post-concussion symptoms has been associated with pre-, peri-, and post-injury psychological distress and risk of psychiatric disorders (PTSD, depression, anxiety, substance abuse, somatoform disorders), anamnesis should also include an assessment of pre-injury and current mental health difficulties (see **Table 2**) (10, 28, 61, 64). Finally, information on social and legal factors, such as availability of social support, life stressors, and involvement in legal proceedings needs to be collected (81).

A variety of symptom checklists exist to assess somatic, emotional, and cognitive post-concussion symptomatology, and require patients to indicate presence, absence, frequency, or intensity/severity of symptoms. Neuropsychological performance based outcomes include measures of attention, memory, concentration, orientation and executive function, and can corroborate subjective complaints of impaired cognition. However, cognitive deficits after mTBI are usually transient (28) and appear to be only weakly related to subjective complaints (23). Standard neuropsychological procedures should be followed to ensure that test results are not influenced by comorbid disorders [e.g., attention deficit hyperactivity disorder, and dyslexia (83, 84)], or inadequate understanding of test and questionnaire requirements, or low effort (85). Currently, only the field of sport concussion utilizes short reliable and sensitive screening instruments (7–10 min) to identify possible symptoms (86). A comprehensive overview of instruments suitable for clinical assessment is presented in **Table 2**. This overview is based on common data elements (CDE) recommendations (87–89) and frequent clinical use.

Neuroimaging and Persistent Post-concussion Symptoms

No consensus has been reached on the relevance of imaging indicators of brain abnormalities for prognosis and outcome after mTBI. **Figure 3** presents magnetic resonance imaging (MRI) images of patients with post-concussion symptoms. Several studies have shown that measures derived from MRI (80, 90–92) or magnetic resonance spectroscopy (MRS) can reveal structural or functional abnormalities in adults and children with an otherwise normal CT (35). Thus, for some patients, persistence of post-concussion symptoms may be explained by yet unknown brain abnormalities. However, current evidence is equivocal and the few large-scale, prognostic studies available suggest only small effects (93), if at all.

Post-concussion Symptoms and Outcome: Health Related Quality of Life, Return to Work, and Societal Costs

Health outcome can be classified along three dimensions: health-related quality of life (HRQoL), functional, and economic outcome. Available studies suggested that post-concussion symptoms correlate with lower levels of life-satisfaction (69, 94) and HRQoL (95). HRQoL measures supplement functional and mental health outcomes with information on how health conditions influence patients' self-reports of their subjective well-being. HRQoL represents an important outcome after TBI, as it provides well-standardized information on the recovery patterns and frequency, nature, severity, and duration of the functional consequences (96). Post-concussion symptoms have been linked to lower levels of satisfaction with life (69) and HRQoL in adults (94) and children (97). However, given the association of pre-injury physical and mental health status with persistent post-concussion symptoms, the specificity of these findings is still unclear. Further research is needed to isolate the specific effects of persistent symptoms on HRQoL (14).

Furthermore, post-concussion symptoms are associated with reduced return to work (69, 98, 99). There is a need to focus

TABLE 2 | Selection of Post-concussion symptoms assessments (adults and children) based on CDE recommendations and frequent clinical use.

Assessments	Examinations and instruments	Population
Clinical Examination and History	Standardized medical history and history of injury event, neurological and physical examination including orientation, speech fluency, memory, concentration, dyslexia, dizziness, vertigo, sleep, cranial nerves, motor, sensory and gait assessment; balance and vestibular testing; respiratory and heart rate, blood pressure; Cervical spine range of motion and tenderness; comprehensive headache assessment; neuroimaging (if mandated by neurological deficits) Standardized pre- and post-injury anamnesis of depression, anxiety, stress, dissociation, behavior, and other mental health problems retro- and prospective assessment: e. g. Structured Clinical Interview-DSM, Mini International Neuropsychiatric Interview (v 5.5), Diagnostic Interview Schedule for Children-IV, Neuropsychiatric Rating Schedule (NPRS), Clinician-administered PTSD Scale (CAPS)	A/P
Self-reported post-concussion symptoms	Health and behavior inventory*	P
	Neurobehavioral symptom inventory**	A
	Post-concussion symptom inventory**	P
	Rivermead post-concussion symptom questionnaire*	A
Neuropsychological Impairments	Behavior rating inventory of executive function**	P
	Rey auditory verbal learning test*	A/P
	California verbal learning test for children*	P
	Delis-kaplan executive function system—verbal fluency*	P
	Immediate post-concussion assessment and cognitive testing**	A/P
	Trail making test (TMT)*	A
	TRAILS-PRESCHOOL**	P
	Cognitive battery-NIH toolbox**	A/P
	Wechsler abbreviated scale of intelligence*	P
	Wechsler adult intelligence scale*	A
	Wechsler intelligence scale for children-iv*/wechsler preschool and primary scale of intelligence -III	P
Psychological and psychiatric status	Brief-symptom-inventory-18*	A
	Beck-depression inventory II**	A/P
	Child behavior checklist**	P
	Patient health questionnaire-9**	A/P
	Screen for Child Anxiety Related Emotional Disorders (SCARED)**	P
	Minnesota Multiphasic Personality Inventory (MMPI)**	A
	Posttraumatic Stress Disorder Checklist (PCL)**	A
	Short Mood and Feelings Questionnaire (SMFQ)**	A/P
	Alcohol Use disorders identification test: self-report version (AUDIT)**	A
Symptom validity	Test of memory malingering (TOMM)**	A/P
	Medical symptom validity test**	A/P
Family and environment	Family Assessment Device (FAD)**	A/P
	Child and Adolescent Scale of Environment (CASE)**	P
	Family Burden of Injury Interview (FBII)**	P

**Common Data Elements (CDEs) recommended as basic measure; **CDEs recommended as supplemental measure; A, Adult TBI; P, Pediatric TBI.*

on the management of persistent post-concussion symptoms to facilitate return to work (100).

The societal costs of TBI include direct medical costs and indirect expenses related to the illness and the value of lost production due to reduced working time or impaired work performance. A large part of the total lifetime costs in the field of TBI are associated with mTBI. The high incidence of mTBI, combined with a large group of patients with long-term post-concussion symptoms, results in a substantial societal and economic burden (101).

Carefully designed longitudinal research on HRQoL, functional recovery, costs and return to work is needed to differentiate persistent deficits and symptoms due to post-concussion symptoms from the effects of pre-injury neuropsychiatric disorders and other factors not associated with mTBI (14).

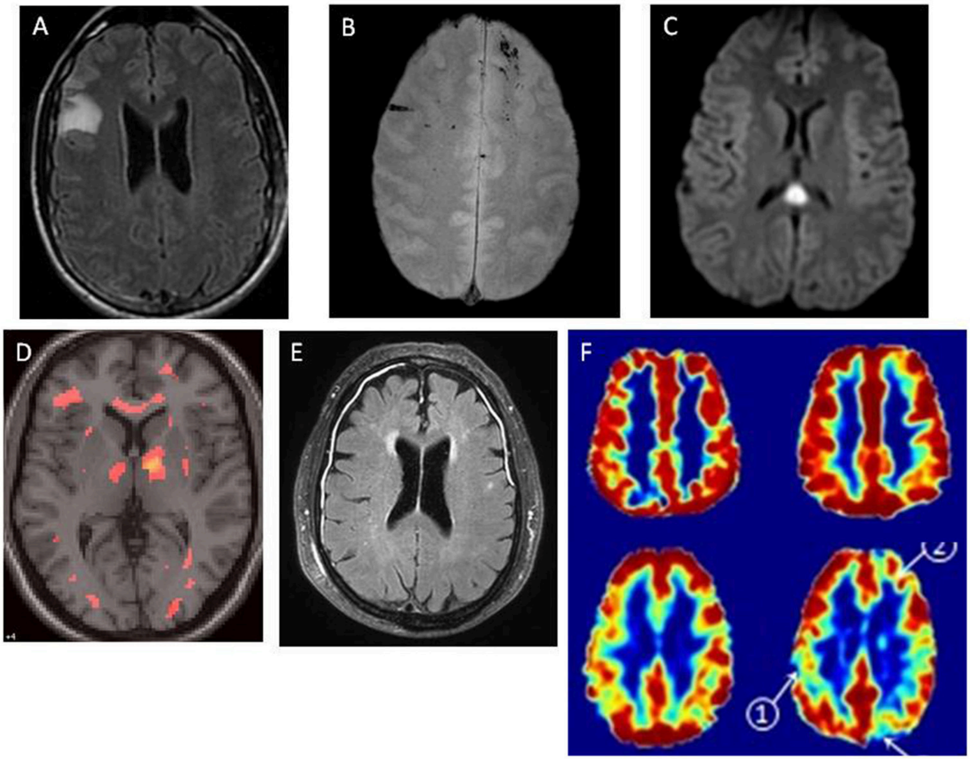

FIGURE 3 | Magnetic resonance images of patients with post-concussion symptoms. MRI findings in patients with mTBI, demonstrating multiple pathologies. In each case, cranial CT was normal. MRI was obtained within 48 h on injury. **(A)** Right frontal non-hemorrhagic contusion, noted on FLAIR image. **(B)** Linear microhemorrhages in left and right frontal lobes, noted on T2* image. **(C)** Diffuse axonal injury lesion in splenium of corpus callosum, with restricted diffusion noted on DWI image. **(D)** Diffuse axonal injury, with multifocal lesions noted on diffusion tensor imaging (DTI). **(E)** Traumatic meningeal enhancement of subdural effusions, noted on post-gadolinium FLAIR image. **(F)** Traumatic microvascular injury.

- Top row represents a single healthy control. Bottom row represents a single TBI patient.
- Left column: Cerebral Blood Flow (CBF), assessed by arterial spin labeling.
- Right column: Cerebrovascular reactivity (CVR) assessed using BOLD response to hypercapnia.

Credit for figures: Figures A, B, C, E: Larry Latour, PhD, NINDS/NIH; D: Carlos Marquez de la Plata, PhD, University of Texas at Dallas; F: Franck Amyot, PhD, Uniformed Services University of the Health Sciences.

MANAGEMENT OF PATIENTS WITH POST-CONCUSSION SYMPTOMS

Pharmacological Interventions

The evidence for pharmacological treatment of depression, anxiety, and mood lability after mTBI is limited and conflicting. A meta-analysis evaluating the effectiveness of depression treatment after mTBI found that studies using a pre-post design suggested treatment benefits from selective serotonin reuptake inhibitors (102). In contrast, the overall effects of controlled trials included in this meta-analysis did not reveal significant differences between treatment and control groups, with some evidence favoring the control condition (102). However, a recently published RCT found sertraline to be effective in preventing depression following TBI when administered early after injury (103). These findings may have considerable therapeutic implications for patients after TBI, but future studies are needed to replicate results before a change in the treatment guidelines could be recommended.

Non-pharmacological Interventions

Evidence concerning the benefits of non-pharmacological interventions targeting post-concussion symptoms is limited. Early educational interventions in ED patients after mTBI may be promising in reducing the incidence and severity of post-concussion symptoms since a single-center RCT focusing on symptom management delivered via telephone counseling demonstrated reduced chronification of post-concussion symptoms during the first 3 months post-injury (104). This finding could not be replicated in a multi-center study; however the investigated patients showed mixed severity of TBI (105).

A recent study suggests that cognitive behavioral therapy (CBT) can improve HRQoL in patients with persistent post-concussion symptoms in the context of outpatient rehabilitation services (106). However, the effect of CBT on post-concussion symptoms was only marginal (106). Problem orientation and problem-solving skills seem to improve by neuropsychological rehabilitation addressing self-regulation of cognitive and emotional processes (107), but evidence is limited.

Evidence for beneficial effects of neuropsychological rehabilitation concerning post-concussion symptoms is limited. A systematic review found evidence that, when applied early, such approaches may be efficient in reducing self-reported post-concussion symptoms, anxiety and depression, but do not result in a clear reduction of cognitive impairment (108).

Intervention studies in children and adolescents are highly variable, of limited methodological quality, and evidence to support any particular intervention for post-concussion symptoms in pediatric samples is absent (109, 110). In adults, as in pediatric populations, well-designed prospective studies focusing on non-pharmacological multidimensional intervention that show improvement on variables such as HRQoL and return to play and work are still lacking.

Rest and Post-concussion Symptoms

Historically, "rest" has been a foundation in the treatment of acute mTBI (70). Concerns have been raised regarding the expert-based consensus recommendation for rest after acute concussion, as studies in adults (111, 112) and children (113) indicate that prolonged rest, longer than 3 days to a week may contribute to prolonged symptomatology (114), and no reduction in post-concussion symptoms was found in a study on rest interventions (115).

Vestibular and Vision Rehabilitation Therapy

The traumatic event resulting in mTBI may also cause concomitant cervical soft tissue damage, resulting in "whiplash-related" symptoms such as headache, dizziness, and balance dysfunction as well as cognitive, vestibular and visual dysfunction (38). A RCT comparing cervical spine physiotherapy and vestibular rehabilitation therapy (VRT) with a control condition in athletes found that among the intervention group, a significantly higher proportion of individuals were medically cleared after 8 weeks of treatment (116). However, a recent systematic review concluded that current evidence for optimal prescription and efficacy of VRT in patients after mTBI is still limited (117). In addition, large retrospective cohorts including both adults and children examining vision rehabilitation for vision disorders associated with mTBI have demonstrated clinical improvement in conditions such as convergence and accommodative insufficiency (118–120). Thus, high-level studies evaluating the effects and optimal intervention window for VRT and vision rehabilitation are required.

Headaches

Headaches are among the most disabling symptoms after mTBI. Most post-traumatic headaches show clinical features of a recognized primary headache, such as migraine headaches or tension headaches. Post-traumatic migraines may respond to the same abortive and prophylactic treatments as sporadic migraines (121). In addition, non-pharmacological approaches such as biofeedback, physical therapy, CBT, either as primary or adjunctive treatments, have also been successfully applied to persistent post-concussion headaches (65, 122).

CONCLUSIONS AND FUTURE DIRECTIONS

Despite a sharp increase in studies investigating post-concussion symptoms, controversies and debates still exists with regard to etiology, diagnosis, classification systems, pathophysiology, natural history, prevalence, and terminology. The subjective nature of post-concussion symptoms, their low specificity, and the significant overlap with other physical, neurological, and psychiatric conditions add additional challenges to these discussions (10, 12, 19, 39, 44, 45, 56, 59, 82). The frequent overlap and idiosyncratic interplay of post-concussion symptoms with pre- and post-injury psychiatric, psychological and social factors are still under-investigated and necessitate a standardized comprehensive differential diagnosis of comorbid mental conditions, in particular depression, anxiety disorders and PTSD.

In this review, we described possible factors contributing to post-concussion symptoms from a bio-psychosocial perspective. Insights into the complex nature of post-concussion symptoms may support the risk estimate of persistent symptoms in individual patients. In addition, it may provide targets for predictive modeling which combine the different factors contributing to post-concussion symptoms. Currently, no valid model is available to predict post-concussion symptoms in adults and children (45, 75). Future predictive modeling studies could be improved by using solid methodology (see **Panel 1**). However, the feasibility of predictive modeling may be debated given the complex, controversial, and multifactorial nature of post-concussion symptoms. Therefore, investing in routine and economic follow-up methods (e.g., smartphone-based experience sampling approaches which have demonstrated feasibility and utility in the post-injury setting (123, 124) might be prioritized over predictive models.

The frequent reliance on simple symptom questionnaires for diagnosis ignores possible biases (10) and the fact that the major classification systems require several other criteria to be fulfilled, such as performance-based evidence of cognitive impairment (21). Most questionnaires were developed in and for patients with more severe deficits, thus their sensitivity and specificity in mTBI may be limited. More refined neuropsychological tests, especially those sensitive enough to assess cognition after mTBI, may support the diagnosis of post-concussion symptoms. Moreover, short screening batteries (computerized and paper and pencil) are needed for use in EDs and in general practice. This is aligned with international attempts at developing and implementing standards for clinical research (e.g., CDEs) (87), terminology and diagnosis criteria for post-concussion symptoms.

The heterogeneous nature of mTBI and post-concussion symptoms and the lack of reliable biological predictors and clinically useful gold-standard biomarkers (34) hamper the development of disease-modifying therapies. A first step may be the identification of specific biochemical (125) and imaging biomarkers that can complement clinical diagnosis, inform prognosis by identifying patients at risk for post-concussion symptom persistence, and predict treatment response (90, 101). Portable, lower-cost imaging modalities such as functional near infrared spectroscopy warrant further investigation to determine their clinical utility in diagnosis and management of mTBI (126).

Large-scale multidimensional, prospective longitudinal studies with several measurement points are strongly required to tackle current challenges in studying post-concussion symptoms. Such designs would allow stratified subgroup analyses to identify patients at risk for developing persistent symptoms, and might help to advance early and personalized treatment. Depending on the research question, improved designs should include control groups to provide insight into the spontaneous recovery, progression, injury severity, frequency, intensity, and fluctuation (trauma controls and healthy participants) of post-concussion symptoms.

Due to normal variation in developmental trajectories, outcomes in children after mTBI may be particularly variable. Longitudinal large sample studies (>100) that investigate predictors of post-concussion symptoms in pediatric populations with multiple endpoints, adequate controls are especially important since high neurologic and cognitive plasticity is present here.

Although evidence for effective treatments is limited, a multi-disciplinary approach corresponding to the complex etiology of post-concussion symptoms may be the most promising. Such an approach would combine in-depth comprehensive medical and neurological diagnosis with an emphasis on psychiatric differential diagnostics and psychosocial und neuropsychological outcome assessment. Future treatment directions (repetitive transcranial magnetic stimulation, vestibular and vision rehabilitation therapy, and aerobic exercise) may offer a solution for the basic pathological processes associated with post-concussion symptoms (65).

Standardization of treatment and interventions, outcome measures (87), and follow-up assessment time-points would enhance reliability and validity of research comparisons and individualized treatment. One might speculate as to whether post-concussion symptoms represent the most valid endpoint for treatment/study after mTBI. Given their low specificity, it may well be that other outcomes (e.g., functional outcome and HRQoL) prove to be more useful.

In this focused review, we only included prospective cohort studies with at least 100 participants, and reviews, with some exceptions (**Appendix A**). Ten included studies did not meet these criteria (20, 29, 30, 39, 40, 57, 72, 83, 84, 127). For these topics, there was no prospective study with at least 100 participants available. Therefore, prospective, multicenter research with larger patient samples is needed. In addition, it should be noted that studies fulfilling our quality criteria might still be at risk of bias. Attrition is a recurrent problem (45, 75), that may have influenced the reported prevalence rates, the relevance of etiological factors and treatment effectiveness. In addition, some studies of etiological factors were based only on univariable analyses, while multivariable assessment is highly recommended because of the multifactorial nature of post-concussion symptoms.

To summarize, standardization of the multidimensional comprehensive diagnostics, treatment interventions, and follow-up assessment time-points may enhance reliability and validity of research comparisons and refine personalized treatment and care. This review documents the need for future studies to target the identification of potential mechanisms, new imaging techniques, comprehensive multidisciplinary assessment and treatment options. Longitudinal, well controlled studies applying standardized diagnostic assessment strategies and evidence-based interventions are needed in adult and pediatric mTBI populations to optimize recovery and reduce burden of post-concussion symptoms.

AUTHOR CONTRIBUTIONS

SP and NvS wrote and revised the manuscript, finalized the paper based on authors, and reviewer feedback. MC conducted the search strategy, screened papers, extracted data of eligible papers, wrote, and revised the manuscript. RD-A, RR, JH, AC, CM, AG, and DV wrote and revised the manuscript. All authors critically reviewed and approved the final version of the paper.

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SUPPLEMENTARY MATERIAL

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Long-Term Return to Work After Acquired Brain Injury in Young Danish Adults: A Nation-Wide Registry-Based Cohort Study

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Objective: (1) To determine patterns of return to work (RTW) after traumatic brain injury and other causes of acquired brain injury (ABI) among young adults aged 19–30 years and (2) to compare the stability of long-term labor-market attachment (LMA) to the background population.

Method: Nationwide registry-based inception cohort study of 10 years weekly data of employment status. Patients ($n = 8,496$) aged 19–30 years with first-ever diagnosis of TBI, stroke, subarachnoid hemorrhage, encephalopathy, brain tumor, or CNS infections during 1999–2015. For comparison, a general population cohort ($n = 206,025$) individually matched on age, sex, and municipality was identified. The main outcome was RTW, which was defined as time to LMA, i.e., a week without public assistance benefits except education grants/leave. Stable labor-market attachment (sLMA) was defined as LMA for at least 75% over 52 weeks. The cumulative incidence proportions of RTW and stable RTW in the ABI cohort were estimated with the Aalen-Johansen estimator with death as a competing event.

Results: Twelve weeks after diagnosis 46.9% of ABI cohort had returned to stable RTW, which increased to 57.4% 1 year after, and 69.7% 10 years after. However, compared to controls fewer had sLMA 1 year (OR: 0.25 [95% CI 0.24–0.27]) and 10 years after diagnosis (OR: 0.35 [95% CI: 0.33–0.38]). Despite significant variations, sLMA was lower compared to the control cohort for all subtypes of ABI and no significant improvements were seen after 2–5 years.

Conclusion: Despite relatively fast RTW only a minor proportion of young patients with ABI achieves sLMA.

Keywords: brain injury, return to work, employment, prognosis, TBI, young adults

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INTRODUCTION

Acquired brain injury (ABI) is by definition an injury to the brain that is not hereditary, congenital, or degenerative, but acquired after birth. ABI constitutes a variety of injuries such as traumatic brain injury (TBI) and non-traumatic causes (non-TBI), where the latter includes stroke, subarachnoid hemorrhage (SAH), CNS infection, encephalopathy, and brain tumor (1). ABI is among the most disabling conditions (2, 3) with potentially profound implications for the individual, family, and society, since it often leads to short- and long-term physical, communicative, cognitive, and emotional dysfunction. Consequently, the capability to return to work (RTW) or resume education (4–6) may be reduced, since it is highly dependent of physical, cognitive, communicative, and emotional functioning.

Young adults often have better functional outcomes after TBI or stroke compared to older adults (7, 8). Nevertheless, younger age is reported as a negative predictor of long-term outcome such as RTW (5, 9). Young adults are often in the process of completing their educational achievements or are in the early stages of their careers. Since ABI may influence or even hamper the ability to complete education or maintain stable labor-market attachment (LMA), young adults may be a particularly vulnerable group (5, 10).

Return to work ability after ABI is largely unknown, but some reports are available for stroke and TBI. For TBI patients irrespectively of age, 30.5% has been reported to RTW 1 year after injury (11), whereas 11.0–59.5% (12) of younger stroke patients RTW. Corresponding figures for SAH were 35.2–71.5% (13, 14), whereas data are limited for patients with brain tumor (15) and unknown for encephalopathy. For TBI, it has been shown that only a minor proportion achieves stable LMA (sLMA) despite the fact that many at some point return to work (5, 16). Furthermore, the cause of injury i.e., TBI or non-TBI is reported not to influence the RTW (11). However, none of these studies are nationwide or compare to an age-matched background population.

The primary objective of this study was to determine the likelihood of RTW after ABI among young adults in Denmark aged 19–30 years for up to 10 years following injury and to compare RTW in different subtypes of ABI. Furthermore, to compare sLMA among ABI patients to the general population.

MATERIALS AND METHODS

Two cohorts were identified using nationwide population-based Danish registries. (1) All Danish patients between 19 and 30 years diagnosed with a first-ever stroke, traumatic brain Injury, brain tumor, encephalopathy, CNS infection, or SAH during the period 1999–2013. (2) A comparison cohort extracted from the general Danish population and individually matched to the ABI patients on age, sex, and municipality.

Setting

In 2015 Denmark had a population of 883,909 young adults aged 19–30 years. Employment rate in this age-group increased with age from 49.3 to 69.3% (17). The government provides financial support in case of sickness or unemployment. Sickness benefits are available for a limited period or until the individual returns to work. A person must be actively job seeking to receive unemployment benefits and the benefits are reduced after prolonged sickness or unemployment. All Danish students regardless of social status are entitled to a state educational grant from the age of 18 years if they attend a youth education program (high school level) or higher education. The healthcare-system in Denmark is primarily publicly funded and all patients with the diagnoses included are exclusively treated by publicly hospitals during the acute phase.

Data Sources

The Danish Civil Registration System holds information on immigration, municipality at index, death, sex, and date of birth for all Danish citizens (18). The unique personal identification number assigned to all Danish citizens was used for accurate individual-level linkage between registries. The Danish National Registry of Patients (DNP) covers all contacts to Danish public hospitals. DNP holds information on all admissions since 1977 and all outpatient contacts since 1994 (19). Diagnoses have been classified according to the International Classification of Disease revision 10 (ICD-10) since 1994.

Employment status was obtained from the DREAM-registry administered by the Danish National Labor-market Authority (20), which provided weekly information of self-support as well as any public transfer payments including state education grants given to all persons aged 18–65 years with a Danish civil registration number. We used the socio-economic background of the participants' mothers. The mothers were identified in the fertility database (21) and subsequently highest attained educational level (basic school, high school, short education, higher education, or unknown) from the Danish Educational attainment Registry (22) and age-adjusted quintiles of disposable income from registries administered by Statistics Denmark were obtained. Finally, cohort members were classified as immigrants, descendants or native Danes by using information from Statistics Denmark (23).

Population

The ABI patients were identified in DNP and were required to have a first-ever diagnosis of brain tumor, CNS infection, encephalopathy, stroke, SAH, or TBI between 1999 and 2013 (**Table 1**). Patients only seen at out-patient clinics were not included. In addition, we excluded cases from the period 1994–1998 to ensure that cases during 1999–2013 were first-ever cases.

The general population comparison cohort was identified using the Danish Civil Registration System by risk set sampling, i.e., controls had to be alive and at risk of first-ever ABI at the date of diagnosis (index) of the corresponding ABI patient.

Abbreviations: ABI, Acquired Brain Injury; CI, Confidence Interval; CNS, Central Nervous System; LMA, Labor-market attachment; DNP, Danish National Registry of Patients; OR, Odds Ratio; RTW, Return To Work; SAH, Subarachnoid Hemorrhage; sLMA, Stable Labor-market attachment; sRTW, Stable Return To Work; TBI, Traumatic Brain Injury.

TABLE 1 | ICD-10 codes.

Diagnosis	ICD-10 code
Stroke	I60-1, I63-4, DI679, DI67-DI68 (-I674), DG46
Traumatic brain injury	S020, S021, S027-S029, S061-S071, S097, T020, T040, T060
Encephalopathy (anoxic/metabolic diseases)	B220, E159, E512, G410, G929, G931, G938, G978, I460, O292, O743, O754, O892, T58, T719, T751, I674, G 372
CNS infections	A321, A390, A398, B003, B004, G040, G042, G048, G05, G060, G07-G09
Brain tumor	C70-C71, D32, D330, D332, D337, D339,

For each ABI patient 25 individuals matched by age (month and year), sex, and municipality at index were selected. The matching factors were chosen a priori to address confounding by age, sex, and regional differences in socio-economic position and unemployment rates. Both patients and controls were required to be residing in Denmark 1 year prior to index. Patients and controls were followed from 12 weeks after index until December 31, 2015, death or emigration, whichever came first.

Study Outcomes

For each week, individuals were defined as self-supportive if no public benefits, except for state education grant, were received or while being on leave. If an individual was self-supportive for at least 75% of 52 consecutive weeks they were considered to have a stable labor-marked attachment (sLMA) (24). This cut-off was chosen to require the individuals to be primarily self-supportive.

For the ABI cohort, time to RTW was defined as the first week of self-supportiveness after baseline (12 weeks after the diagnosis). Time to stable return to work (sRTW) was defined as the time from baseline to the first week followed by of a 52-week period with self-supportiveness in at least 75% of the period.

Statistical Analysis

SLMA for the ABI-cohort was compared with the general population cohort at 1, 2, 5, and 10 years after baseline by conditional logistic regression accounting for the matching and corresponding odds ratios (OR) and 95% confidence intervals (CI) estimated. Two types of adjustment were done (1) according to the matching (simple adjustment) and (2) with further adjustment for sLMA 1-year prior to index, immigration status, mothers' income and mothers' highest achieved educational level (full adjustment). Individuals that had died or emigrated at a given time-point were excluded from that analysis. In addition, we only considered complete cases, however, treating missing values as a separate category, did not change the estimates materially (data not shown). Furthermore, we did two sensitivity analyses: (1) excluding cases identified only through emergency room contacts and (2) using alternative cut-offs for defining stable LMA, i.e., >50 and >90%, respectively.

The cumulative incidence proportions of RTW and sRTW in the ABI cohort were estimated with the Aalen-Johansen estimator with death as competing event (25). Significance level was set to 5% and all analysis were performed in "R version 3.2.3" (26). The study was approved by the Danish Data Protection Agency. Ethical approval or individual consent was not required for this type of study by Danish legislation.

TABLE 2 | Descriptive characteristics.

Variables	ABI cohort		Control cohort		
	N	%	*N*	%	*p*-value
Total	8,496		206,025		
Female sex	3,189	37.5	77,040	37.4	
Mean age at diagnose (sd)	24.40	3.54	24.40	3.55	
Overall					
Brain tumor	480	5.6	11,642	5.7	
CNS infection	634	7.5	15,317	7.5	
Encephalopathy	829	9.8	20,075	9.8	
SAH	575	6.8	13,915	6.8	
Stroke	1,333	15.7	32,285	15.7	
TBI	4,645	54.7	112,794	54.7	
Self-supportive 1 year before injury	5,677	66.8	168,326	81.7	<0.001
Mother's disposable income					<0.001
0–20%	1,810	21.3	35,556	17.3	
20–40%	1,552	18.3	34,909	16.9	
40–60%	1,409	16.6	36,803	17.9	
60–80%	1,518	17.9	39,879	19.4	
>80%	1,481	17.4	39,160	19.0	
Missing	726	8.5	19,721	9.6	
Highest educational level of mother					<0.001
Basic school	2,915	34.3	61,455	29.8	
High school	212	2.5	5,236	2.6	
Low education (incl vocational education)	2,841	33.4	71,915	34.9	
Higher education	1,576	18.5	43,485	21.1	
Missing	952	11.2	23,910	11.2	
Immigration status					<0.001
Danish	7,614	89.6	182,779	88.7	
Descendants	667	7.9	18,648	9.1	
Immigrants	215	2.5	4,601	2.2	

RESULTS

Descriptive Data

Of the 8,496 patients who met the inclusion criteria, 4,645 (54.7%) had TBI, 1,333 (15.7%) had stroke, 575 (6.8%), had SAH, 829 (9.8%) had encephalopathy, 634 (7.5%) had CNS infection and 480 (5.6%) had brain tumor. Some differences were seen between the ABI cohort and controls (**Table 2**). Both the mother's income and educational level were lower in the ABI cohort. The proportion of immigrants and descendants were significantly higher in the ABI cohort compared to the general population cohort. During the study 393 (4.6%) died and 398

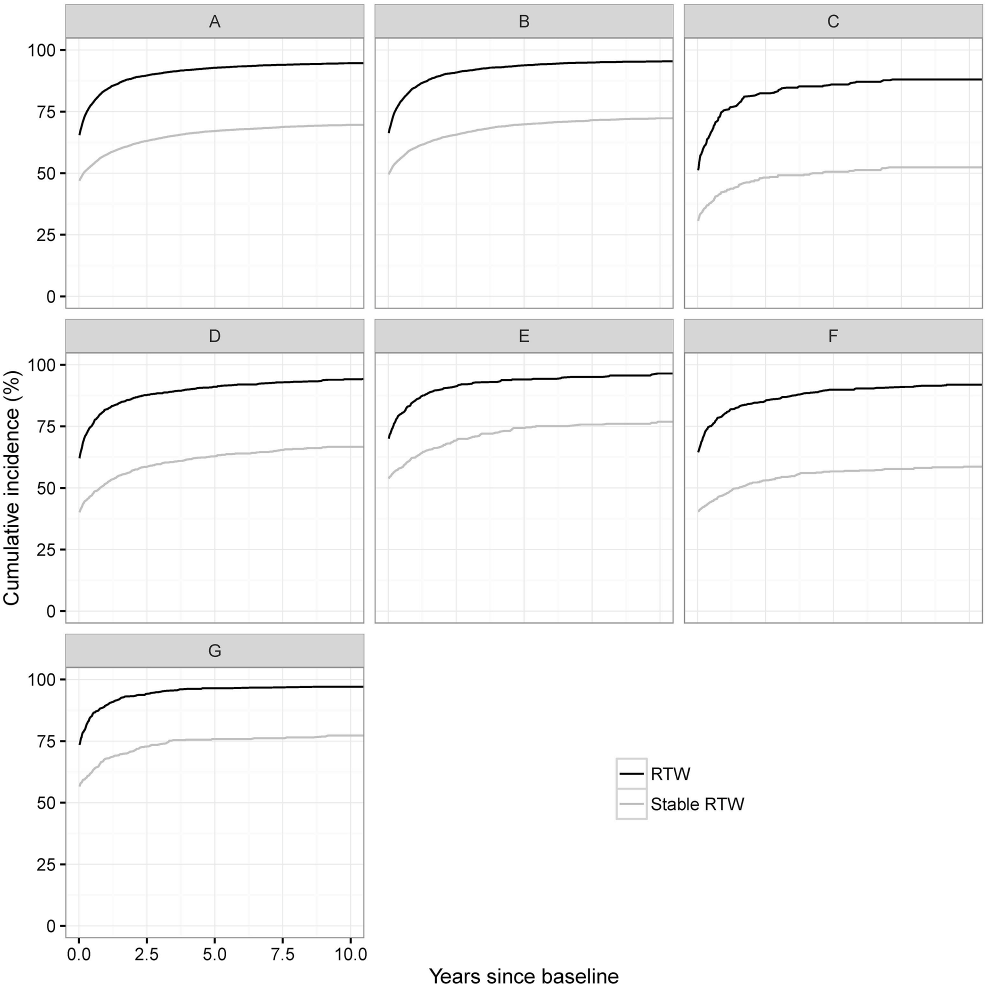

FIGURE 1 | Cumulative incidence of RTW and sRTW according to type of brain injury: **(A)** ABI cohort, **(B)** TBI, **(C)** Brain Tumor, **(D)** Stroke, **(E)** SAH, **(F)** Encephalopathy, and **(G)** CNS infection.

(4.7%) emigrated within the ABI cohort, whereas 1,151 (0.6%) died and 12,258 (5.9%) emigrated within the comparison cohort.

Return to Work

The cumulative incidences of RTW and stable RTW are shown in **Figure 1** and in **Supplementary Table 1**. Across diagnoses 50–75% had returned to work at baseline, the corresponding numbers for sRTW were 30–60%. Overall, the cumulative incidence of sRTW mainly increased during the first 5 years, while RTW and sRTW reached levels between 88–95 and 55–80% after 10 years for RTW and sRTW, respectively. Brain tumors had the lowest cumulative incidence of stable RTW followed by encephalopathy, and stroke, whereas CNS infection had the highest proportion of RTW and stable RTW followed by SAH and TBI. Persons with sLMA 1-year prior to index had a higher likelihood of stable RTW (data not shown). Excluding emergency room cases gave slightly lower RTW and sRTW however with similar patterns as in the main analysis (data not shown).

Labor-Market Attachment

Simple and fully adjusted odds ratios for sLMA for the ABI cohort compared to the matched controls are given in **Table 3**. The fully adjusted odds ratio for 1 year ($\text{aOR}_{1\text{YR}}$), 2 years ($\text{aOR}_{2\text{YR}}$), 5 years ($\text{aOR}_{5\text{yr}}$), and 10 years ($\text{aOR}_{10\text{yr}}$) are shown in **Figure 2**. The proportion of the control cohort with sLMA was 77.4–85.7% throughout the follow-up period (**Table 3**). In the ABI cohort 52.9% had sLMA 1 year after baseline, which was significantly lower compared to the control cohort ($\text{aOR}_{1\text{yr}}$: 0.25 [95% CI 0.24–0.27]). Ten years after baseline the proportion of sLMA in the ABI cohort had increased slightly to 53.2% but remained significantly lower compared to the controls ($\text{aOR}_{10\text{YR}}$ 0.35 [95% CI: 0.33–0.38]). Despite significant variations in the proportion of patients with sLMA between diagnoses, sLMA remained significantly lower compared to the control cohort for all diagnoses. Most of the diagnoses (i.e., TBI, SAH, stroke, encephalopathy, and CNS infections) showed no improvements in LMA from 2 to 5 years after baseline. However, after 2 years CNS infections had the highest OR for

TABLE 3 | Stable labor market attachment 1–10 years after ABI diagnosis.

	1 year before index		1 year after baseline								2 years after baseline							
Diagnosis	**ABI n (%)**	**Controls *n* (%)**	**ABI *n* (%)**	**Controls *n* (%)**	**Crude OR**	**Crude 95% CI**		**Adj OR**	**Adj. 95% CI**		**ABI n (%)**	**Controls *n* (%)**	**Crude OR**	**Crude 95% CI**		**Adj OR**	**Adjusted 95% CI**	
ABI	5,848 (66.3)	181,128 (81.7)	4,433 (52.93)	175,801 (80.61)	0.26	0.25	0.27	0.25	0.24	0.27	4,534 (55.95)	169,167 (79.8)	0.31	0.29	0.32	0.35	0.33	0.37
TBI	3,292 (68.8)	99,675 (82.3)	2,543 (55.35)	96,680 (81.9)	0.28	0.26	0.29	0.27	0.25	0.30	2,590 (58.23)	93,011 (80.4)	0.33	0.31	0.35	0.36	0.33	0.39
Brain tumor	327 (65.7)	9,892 (80.6)	173 (37.7)	9,621 (79.5)	0.14	0.12	0.18	0.11	0.09	0.14	182 (43.0)	9,251 (79.1)	0.19	0.16	0.24	0.17	0.13	0.21
SAH	417 (70.1)	12,065 (81.1)	337 (59.0)	11,757 (80.4)	0.33	0.28	0.39	0.30	0.23	0.37	345 (61.7)	11,267 (79.2)	0.41	0.34	0.49	0.47	0.37	0.58
Stroke	898 (64.2)	27,875 (80.5)	627 (47.5)	27,122 (79.7)	0.22	0.19	0.24	0.20	0.18	0.24	664 (52.1)	26,097 (78.8)	0.28	0.25	0.32	0.31	0.27	0.35
Encephalopathy	444 (49.5)	18,390 (80.8)	364 (44.9)	17,846 (79.8)	0.19	0.16	0.22	0.27	0.22	0.33	354 (45.2)	17,232 (79.2)	0.2	0.17	0.23	0.30	0.25	0.37
CNS infection	470 (72.2)	13,231 (82.3)	389 (62.6)	12,775 (80.7)	0.38	0.32	0.45	0.37	0.29	0.46	399 (65.7)	12,309 (80.0)	0.47	0.40	0.57	0.53	0.43	0.66

	5 years after baseline								10 years after baseline							
	ABI n (%)	**Controls n (%)**	**Crude OR**	**Crude 95% CI**		**Adj OR**	**Adjusted 95% CI**		**ABI n (%)**	**Controls n (%)**	**Crude OR**	**Crude 95% CI**		**Adj OR**	**Adjusted 95% CI**	
ABI	3,457 (54.95)	130,952 (78.8)	0.32	0.31	0.34	0.37	0.35	0.40	1,872 (53.16)	74,033 (78.0)	0.32	0.29	0.34	0.35	0.33	0.38
TBI	1,980 (56.1)	72,410 (79.1)	0.33	0.31	0.36	0.38	0.35	0.41	1,028 (51.78)	40,980 (78.0)	0.3	0.27	0.33	0.33	0.30	0.37
Brain tumor	125 (46.1)	7,026 (78.8)	0.22	0.17	0.28	0.23	0.17	0.30	66 (49.1)	4,090 (78.9)	0.24	0.17	0.34	0.34	0.23	0.51
SAH	283 (62.6)	9,090 (79.3)	0.43	0.35	0.52	0.49	0.38	0.62	168 (58.5)	5,645 (78.00)	0.38	0.30	0.48	0.39	0.29	0.53
Stroke	496 (50.4)	20,014 (78.0)	0.28	0.25	0.32	0.31	0.27	0.37	270 (52.6)	10,527 (77.4)	0.32	0.26	0.38	0.34	0.28	0.42
Encephalopathy	269 (44.5)	13,443 (78.5)	0.21	0.18	0.25	0.32	0.26	0.39	171 (48.6)	7,635 (85.8)	0.26	0.21	0.32	0.36	0.28	0.47
CNS infection	304 (68.0)	8,969 (78.2)	0.59	0.48	0.73	0.65	0.51	0.83	169 (67.9)	5,156 (77.9)	0.6	0.45	0.79	0.61	0.44	0.84

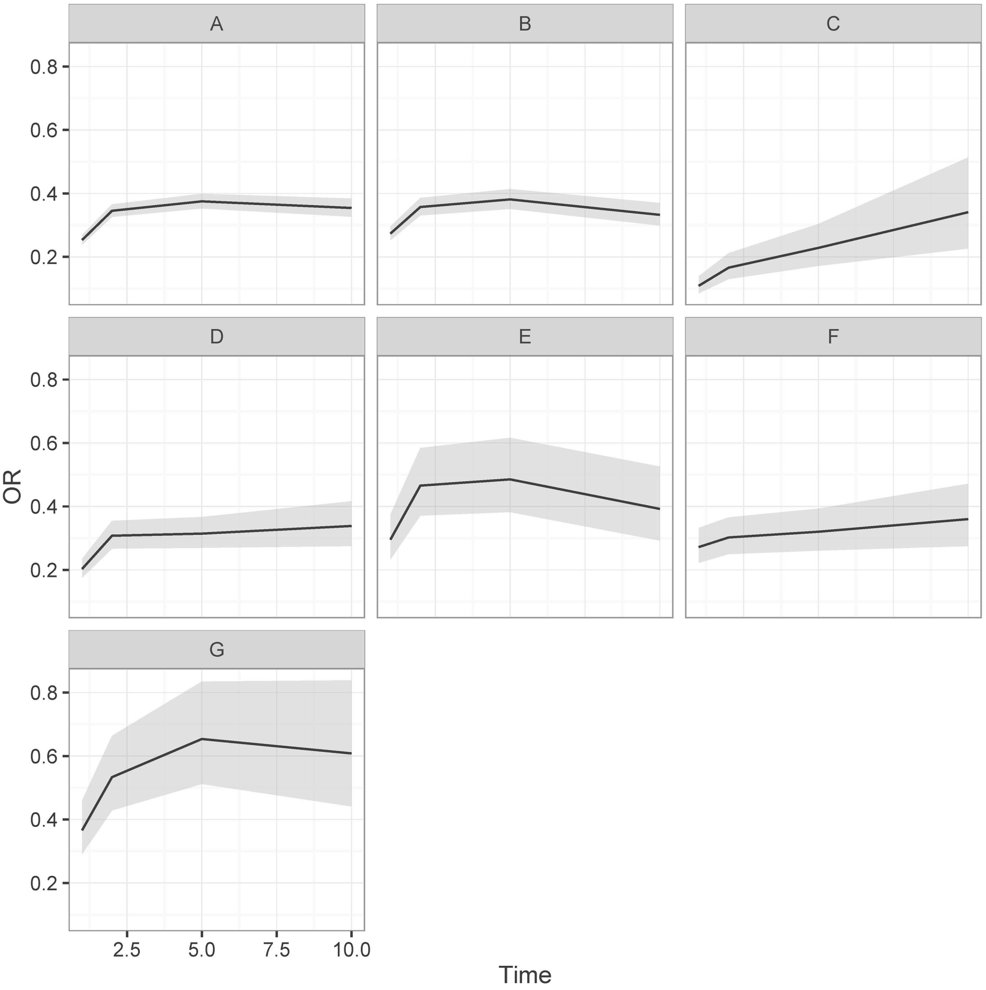

FIGURE 2 | Adjusted odds ratio and CI (gray area) for stable labor market attachment for ABI cohort compared to matched controls: **(A)** ABI cohort **(B)** TBI, **(C)** Brain Tumor, **(D)** Stroke, **(E)** SAH, **(F)** Encephalopathy, and **(G)** CNS infection.

sLMA compared to control cohort (aOR_{2YR}: 0.53 [95% CI: 0.43–0.66]), followed by SAH (aOR_{2YR}: 0.47 [95% CI: 0.37–0.58]), TBI (aOR_{2YR}: 0.36[95% CI: 0.33–0.39]), stroke (aOR_{2YR}: 0.31 [95% CI: 0.27–0.35]), encephalopathy (aOR_{2YR}: 0.30 [95% CI: 0.25–0.37]), and brain tumor (aOR_{2YR}: 0.17 [95% CI: 0.13–0.21]). In the sensitivity analyses of defining sLMA using 50 and 90% cut-offs, respectively, no significant changes were seen (data not shown). Similarly, excluding emergency room contacts yielded similar conclusions (data not shown). Only SAH had lower ORs after excluding emergency room contacts (aOR_{5YR}: 0.32 [95% CI: 0.23–0.45]) and when defining sLMA using 50% as cut-off (aOR_{5YR}: 0.39 [95% CI: 0.30–0.50]), respectively.

DISCUSSION

This study shows that ABI has a major impact on RTW and especially on sLMA even 10 years after ABI. Overall, the proportion of ABI patients with sLMA increases until 2 years post-injury with no further significant improvement thereafter. One major exception was, however, for brain tumor patients, who showed increasing sLMA even in the subsequent years. Even though up to 95% of the ABI cohort return to work or education, and up to 77% achieve 1 year of sLMA at some point during the 10 years follow up, only half of the ABI cohort have sLMA after 10 years. This study is, to our knowledge, the first to present nationwide data on RTW and sRTW, as well as sLMA for young adults covering the full spectrum of ABI. Most studies only report data for TBI patients and to a lesser extent stroke. Furthermore, most published RTW studies use a cross-sectional design, which is a design that may not fully capture absence of sLMA. Additionally, direct comparison should be performed with caution, because of substantial differences in setting, case ascertainment, study design, data collection, and outcome definitions across studies (27, 28).

With regard to TBI, large variations (between 30 and 65%) in the proportion that RTW after brain injury (11) have been reported. In settings, comparable to Denmark, studies from Australia and Norway have reported markedly lower levels of RTW compared to our results with RTWs between 45 and 55%, respectively (16, 29, 30). However, patients in the Australian and Norwegian studies were recruited from intensive care units or rehabilitation facilities and are therefore probably more severe cases, whereas we included all cases (including mild cases) in Denmark. The diverging results are thus most likely explained by differences in severity and that this study only considers young adults.

For stroke, specific data regarding the young adults are even more sparse than for TBI. Much in line with our results, a comprehensive review showed that the majority of the stroke patients return to work within the first year, and often within the first 3–6 months (28). However, patients included the entire working age spectrum and large variations with respect to age were reported (19–73%). A Swedish study reported that 74.4% of 18–34 year-old stroke patients had returned to work (both full-time and part-time considered) and the majority within the first 12 months after the stroke (31). This result is higher than that found in our study, and is probably caused by different definitions of RTW.

For patients with glioblastoma the proportion that RTW after 1 year has been reported to be 27% (15), which is lower compared to RTW for brain tumor patients in our study. This difference is likely caused by the higher mortality and higher levels of impairments following glioblastoma compared to the less aggressive tumors that predominates in our young cohort. Also, this may suggest that brain tumors in this age-group often cause a gradually progressing brain injury than the remaining diagnoses considered in this study. On the other hand our results are in line with a British study, which reported a RTW proportion of 52% in a cohort of brain tumor patients recruited from a rehabilitation facility (32).

To our knowledge no reports have presented results of the cumulative incidence of sRTW after ABI. Some studies have explored sLMA after TBI (5, 16, 33) and found that a significant proportion of those who RTW have unstable LMA. This finding is in line with our results, where we found a similar tendency for all diagnoses considered. In a review by van Velzen et al. the authors concluded that the level of RTW was similar for traumatic and non-traumatic ABI after the initial first year (11). However, in this study we found important differences in RTW between the diagnoses that constitute non-traumatic ABI, namely that brain tumor, encephalopathy and CNS infections were significantly different from TBI in terms of RTW. All three subgroups are, however, small compared to the stroke group, and a pooled analysis of non-traumatic ABI group would tend to be dominated by stroke patients.

Although most developed countries provide sickness benefit, comparison across countries should be done with caution due to country-specific requirements and level of compensation. Despite the favorable Danish benefits, individuals are nevertheless focused on returning to work since sickness benefits are only available for limited time. It is therefore notable that despite the relatively favorable conditions for long-term sickness compared to other countries, RTW is nevertheless relatively high in Denmark.

Study Limitations

The main strengths of our study are the nation-wide design, the use of a comparison cohort and the long-term data of public benefits. Furthermore, the unique Danish personal identification number enabled us to link accurately between medical data and employment data. Nonetheless, registry studies are at risk of misclassification and in the current study we relied on the accuracy of discharge-diagnoses and DREAM-data. The discharge data are generally of high quality, however only the validity of stroke and specific CNS infections are known (19). For both diagnoses some misclassification may have occurred in up to 15–20% of the diagnoses and for emergency room contacts even higher (34). However, excluding emergency room contact gave similar patterns although slightly lower LMA. Employment data were retrieved from DREAM, which can elucidate the dynamics of RTW because of the weekly individual registrations (24). Data in the registry have a high positive predictive value (20, 35), however, only sick leaves longer than 2 weeks are registered if the employer claims a reimbursement fee (20). Also, misclassification may have occurred for persons living on own assets or support from family, but this is rare in Denmark. Preexisting comorbidity may also decrease RTW, but to overcome this bias, we adjusted for sLMA prior to index to account for pre-injury differences in LMA between the cohorts. Another limitation to this study is that we did not have information on the severity of ABI. Largely, because there is no uniform measure of injury severity across different types of ABI and such information was not systematically registered for all the included diagnoses in Denmark. In addition, structural factors such as economic recession and structural changes in the Danish health care sector might also have influenced the results. But these factors were not likely to influence the results because the OR for sLMA stratified by year of diagnosis showed no significant differences (data not shown). Furthermore, we might have overestimated the 5- and 10-year estimates for LMA among brain tumor patients, since in contrast to the rest of the ABI cohort, the mortality after brain tumor increases even 5–10 years after index leaving primarily individuals with less severe impairments. A significant proportion of the diagnoses included in this study is associated with low social status (36, 37), which also influences the ability to RTW and subsequent sLMA. Thus, one may overestimate the impact of brain injury if this selection bias is ignored. This problem was addressed by matching and adjusting for social status and consequently we believe this bias is small. Furthermore, socio-economic background of the participants' mothers was used since the socio-economic position of a young adult may be better reflected by the mother's data than by the person's own data in this age-group. However, we cannot rule out some degree of residual confounding, but it is unlikely that it explains the difference in sLMA in ABI patients and their population controls. Finally, the cut-off for sLMA of 75% favors a conservative estimate of the impact of ABI on the ability to assume work.

CONCLUSION

This study demonstrates that a large proportion of young ABI patients return to work within 1 year following brain injury, whereas many fail to achieve long-term sLMA. Young brain tumor patients, however, appear to steadily increase long-term LMA. These findings underline that vocational rehabilitation following acquired brain injury is a long-lasting rather than just a temporary effort to maintain labor market attachment.

AUTHOR CONTRIBUTIONS

MT, LK, SJ, CD, and HF designed and planned the study. MT and CD assembled the data, performed the statistical analyses, and drafted the manuscript. All authors discussed the results and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01180/full#supplementary-material

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Measuring Neurobehavioral Disabilities Among Severe Brain Injury Survivors: Reports of Survivors and Proxies in the Chronic Phase

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Background: Neurobehavioral disability (NBD) has a major influence on long-term psychosocial outcome following acquired brain injury, as it affects not only the survivor of the brain injury, but the whole family.

Objectives: To investigate (1) the frequency of NBD among survivors of severe brain injury measured by the Danish version of the St Andrew's-Swansea Neurobehavioural Outcome Scale (SASNOS) rated by patients and proxies, (2) factors associated with NBD, and (3) concordance between reports of NBD completed by patients and proxies.

Methods: SASNOS was administered at an outpatient unit as a part of a follow-up assessment after discharge from intensive neurorehabilitation. SASNOS consists of five factors describing the following domains: Interpersonal Behavior, Cognition, Aggression, Inhibition and Communication, and both the patient and a proxy were asked to complete the questionnaire. Data collection was conducted over a period of 2 years, and 32 patients and 31 proxies completed the questionnaire. Mean time since injury was 19.4 months (10.0 SD). Most patients were male (68.8%), and most proxies were female (58.1%). Most of the patients had suffered a traumatic brain injury (68.8%).

Results: A fourth of this patient group reported themselves below the normal range on the major domains of Interpersonal Behavior and Cognition. Significant associations between proxies' reports and time since injury, cohabitant status, and the patient's score on the Extended Glasgow Outcome Scale were found. Furthermore, significant differences were found between patient and proxy ratings. Proxies rated patients as having fewer problems on the Interpersonal Behavior domain, and more problems in relation to Cognition. Cognition was the only domain, where patients rated themselves higher indicating fewer problems, compared with their proxies. On both the Aggression and Communication domains, proxies rated patients higher indicating fewer problems than the patients themselves.

Conclusion: Danish brain injury survivors experienced NBD as measured by SASNOS. Differences were found between patient and proxy ratings in relation to Cognition and Interpersonal Behavior. The NBDs identified can affect the survivor's ability to reintegrate and participate in activities of daily living, emphasizing how a systematic assessment is required.

Keywords: neurobehavioral disability, traumatic brain injury, acquired brain injury, SASNOS, chronic phase, proxy ratings

INTRODUCTION

Survivors of acquired brain injury (ABI) often experience severe long-term consequences across physical, cognitive, social, behavioral, or psychological domains. Physical or cognitive disabilities can be devastating, but it has been argued that change in neurobehavioral functioning is one of the most distressing legacies of ABI (1, 2). Neurobehavioral disability (NBD) is a term used to describe these neuropsychological and neurological disabilities in behavior amongst ABI survivors (1, 3–5). The concept of NBD was developed to understand and treat the debilitating psychosocial consequences of severe brain injury. NBD comprises weaknesses of attention control, reduced self-awareness, executive dysfunction, lack of insight, problems in social judgements, labile mood, reduced ability to control impulses, and changes in personality (4–6). Poor attentional control can, in itself, contribute to cognitive problems such as difficulties in prospective memory, and executive dysfunctions, contributing to poor self-awareness, difficulties with social judgments, and reduced inhibitory control of emotions and behavior (7–9). Long-term social isolation and poor psychosocial outcome can be a result of these severe consequences (10, 11). Neurobehavioral outcome and the alterations in such behaviors are complex, as they are not only caused by damage to the brain, but also from interaction with the (a) environment, (b) premorbid personality traits, and (c) post injury learning (5, 7, 12, 13). Kreutzer et al. has argued that the presence of NBD is directly associated with poor outcome (10), and Testa et al. found that neurobehavioral problems and impaired family functioning were strongly related (14). However, even though NBD has been shown to be strongly associated with poor outcome in patients and their families (1, 2, 10, 11), increasing caregiver burden and imposing constraints on community independence (15), it is not an easy form of disability to measure, largely because the pattern of disability can be influenced by many components that vary over time. However, it is important to understand these components as they not only affect the long-term wellbeing of the patient, but the whole family (1, 2, 5, 16–18).

The impact of cognitive disabilities in real life situations is not always paralleled by cognitive impairments captured by neuropsychological tests. The structure and composition of tests used in clinical testing mean that some important observations of neurobehavioral disabilities are missed (5, 19–21). The need to identify neuropsychological features of acquired brain injury that are likely to have an adverse psychosocial impact has therefore culminated in a recognition to develop a measure that can capture characteristics of NBD. This includes the ways they affect social functioning and how they interact with the environment and personal traits (12, 13, 19). Furthermore, it has been recognized that a measure of NBD needs to include both a patient and proxy rating, as some patients lack awareness of their disabilities (22).

One method of measuring NBD has been developed by Alderman, Wood and Williams, who introduced St Andrew's-Swansea Neurobehavioral Outcome Scale (SASNOS) (5). SASNOS was specifically designed for patients with ABI and is based on the WHO International Classification of Functioning, Disability and Health (ICF) framework, classifying behavioral problems that have robust psychometric properties. Furthermore, SASNOS was created based on a comprehensive literature review of the existing scales, which highlighted the importance of an instrument being able to identify NBD and long-term psychosocial outcome. SASNOS consists of five factors describing the following domains: Interpersonal Behavior, Cognition, Aggression, Inhibition, and Communication. The raw scores of SASNOS are transformed into T-scores, which can be compared to healthy controls. A T-score <40 has been used as a clinical cut-off indicating a need for rehabilitation in the specific domain (6). One of the advantages of using SASNOS is that both a patient and a proxy version is available. The proxy version can be completed by both close family members, but also by rehabilitation professionals with comprehensive knowledge about the patient's condition. This is important because some patients experience a lack of awareness of disabilities, thereby underreporting the frequency, severity or significance of specific neurobehavioral problems, compared to proxies (8, 9, 23). Furthermore, studies have indicated that concordance between patient vs. proxy ratings varies across functional domains. Specific items related to self-care or physical function seem to reach high levels of agreement, whereas emotional and behavioral changes seem to be perceived differently by proxies and patients (1, 24, 25). These results support the importance of including an informant or a proxy, e.g., a close relative in the reporting of NBD.

When survivors of severe ABI are seen for follow-up visits after intensive neurorehabilitation, subjective and qualitative reports of NBD by family members frequently occur (25). Due to the lack of ability of standard neuropsychological testing to capture NBD, the present study was designed to quantify these reports systematically by using a validated and reliable measure of NBD. The objectives of the study were to investigate:

a) The frequency of NBD among severe brain injury survivors measured by the Danish version of SASNOS as rated by patients and proxies.
b) If NBD reports were associated with factors related to patient or proxy.
c) Concordance between reports of NBD completed by patients and proxies.

Based on the existing international literature, we hypothesized that the majority of severe ABI survivors would report the presence of NBD in more than one domain, as would their proxies. We hypothesized that factors related to the injury would be associated with both proxies and patients reports of NBD. Furthermore, we hypothesized that discrepancies would be found between reports of patients and proxies, more specifically, that proxies would report more problems than patients in relation to emotional and behavioral disabilities.

MATERIALS AND METHODS

Procedure

After discharge from sub-acute intensive neurorehabilitation in hospital, patients and their close family members were invited for a follow-up visit 1 to 3 years post injury at the outpatient clinic, Department of Neurorehabilitation, TBI Unit, Rigshospitalet, Denmark. During the study period, from December 2015 to December 2017, SASNOS was administered as a part of the standard follow-up assessment. The questionnaire was administered to both the patient and a proxy, in most cases a family member, by a neuropsychologist or a nurse working in the outpatient clinic. The participants were instructed to return the questionnaire when completed, and if the questionnaire was not completed immediately, they were asked to complete it at home and return it in a stamped address envelope.

Patients were included if they met the following criteria:

(1) severe traumatic or non-traumatic brain injury followed by intensive neurorehabilitation at Department of Neurorehabilitation, TBI Unit; (2) $\geq$18 years at time of follow-up; (3) $\geq$1year since time of injury; (4) intact ability to understand and read Danish; (5) $\geq$7 on the Rancho Los Amigos Scale (RLA) at follow-up indicating the resolution of post-traumatic amnesia (PTA) or similar state of confusion for patients with non-traumatic injuries.

For the proxies, the following criteria had to be met: (1) close family member to the patient; (2) $\geq$18 years at time of follow-up; (3) able to understand and read Danish.

Patients and proxies were excluded if they: (1) had an active substance abuse; (2) had severe aphasia; (3) had severe disorders of consciousness or cognitive disabilities that were too severe to complete the questionnaire.

When the study period was completed, 78 patients had been invited for a follow-up assessment at the outpatient clinic. Of these, 2 never showed up. Of the remaining eligible 76 patients, 18 were excluded due to: aphasia ($n = 5$); not able to understand Danish ($n = 1$); severe cognitive disabilities or disorders of consciousness ($n = 10$); did not have any close proxy ($n = 1$); schizophrenia ($n = 1$). Of the remaining 58 patients who fulfilled our inclusion criteria, a few refused to complete the questionnaire ($n = 2$), but most never returned or received the questionnaire ($n = 21$). Consequently, we received 35 patient ratings. Of these ratings one patient questionnaire was returned anonymously, consequently this was excluded from further analyses. Two patients participated in the follow-up twice and completed the questionnaires both times. Only their first response was included in this study. One patient did not permit his proxy to complete SASNOS, and only the response of the patient was registered. Consequently, we ended up with a sample consisting of 63 questionnaires were included for the analyses, including 32 patient ratings and 31 ratings completed by proxies. This is equal to a response rate of 55.2%.

The study was conducted in concordance with the Helsinki Declaration. Patients and proxies were informed orally and in writing about the purpose of the study and that participation was voluntary before providing consent. Furthermore, that data from the study would be presented in anonymous form without any possibility to recognize the individual participants. Data was handled according to the legislation of the Data Protection Agency, and the Database of Highly Specialized Neurorehabilitation Eastern Denmark has been approved by The Danish Health Data Authority (no. 2012-58-0023).

Measures

Descriptive data, comprising age at injury, sex, type of injury, time since injury relationship to proxy, and cohabitant status, were collected from the clinic's local database (Database of Highly Specialized Neurorehabilitation Eastern Denmark). Furthermore, length of post-traumatic amnesia (PTA) or confusion was used as an indicator of the severity of the brain injury. A score on the Glasgow Outcome Scale Extended (GOSE) indicated level of global outcome at time of follow-up. If any demographic or injury related data were missing from the local database, the information were retrieved from the patient's file, thereby eliminating any missing data. All questionnaires were investigated for missing data. In case of missing data from one SASNOS subdomain, the mean value, based on the other items from that specific subdomain, was inserted.

PTA/length of confusion: PTA is defined as a period of loss of consciousness and an inability to make consistently new memories after a brain injury. When a patient is consistently oriented and able to remember day to day and make new memories, the resolution of the PTA or confusional state is complete. The length of time a patient remains in PTA or confusional state is a method to assess the severity of the brain injury and is associated with outcome. A duration of PTA of >28 days is considered as a severe brain injury (26, 27).

GOSE: GOSE is an 8-level scale assessing the global outcome after brain injury. The scores indicate: 1 (dead), 2 (vegetative state), 3 (lower severe disability and completely dependent on others), 4 (upper severe disability and some dependency on others, but can be alone for 8 h), 5 (low-moderate disability, living independently, and working at a low level of performance/performing sheltered work), 6 (upper-moderate disability and returning to previous work with adjustments), 7 (low-good recovery with minor consequences of physical or mental deficits), 8 (upper-good recovery, i.e., full functional recovery) (28, 29). It was used to indicate outcome at time of follow-up.

SASNOS: The main outcome measure used in the study was SASNOS, which consists of five major domains measuring NBD following an acquired brain injury: Interpersonal Behavior, Cognition, Inhibition, Aggression, and Communication. Each of the major domains consist of a number of subdomains, which are shown in **Table 1**.

All 49 items are scored on a seven-point Likert-scale from "never" to "always." Ratings are transformed to standard scores. T-scores with a mean of 50 and standard deviation of 10 is used. Higher scores reflect greater perception of ability and fewer symptoms of neurobehavioral disabilities. Transformation to T-scores allows for cross-scale comparisons and comparisons to neurological healthy individuals. If a patient receives a score of 2 SD (30) from mean of 50 it is statistically significant but if a patient receives a score of 1 SD (31) it is also of clinical interest. Consequently, a clinical cut-off of 40 has been suggested (6). SASNOS consists of two versions; one for proxies or professionals who know the patient well, and another completed by the patient. Good internal consistency has been reported previously with Cronbach's alphas from 0.62 to 0.93 (5) and satisfactory test-retest (0.82–0.96), good inter-rater reliability (0.59–0.83) has also been reported (6).

The questionnaire was translated into Danish following the recommendations for the cross-culture adaption of health status measures, a standardized procedure with back-translation (30) with permission from the original authors (5). Before the start of the present study, the Danish version of SASNOS was piloted by asking 4 patients and 4 proxies to complete SASNOS to investigate if there were any problems in understanding the questions after the translation. This resulted in a modification of the wording in four questions to increase understanding, and these modifications were approved by the original authors.

TABLE 1 | Major domains, sub-domains and number of item on SASNOS.

Major domains	Subdomains	Number of items
Interpersonal behavior	Social interaction	5
	Relationships	5
	Engagement	5
Cognition	Executive functioning	6
	Attention and memory	6
Inhibition	Sexual inhibition	3
	Social inhibition	3
Aggression	Provocative behavior	5
	Irritability	4
	Overt aggression	3
Communication	Speech and language	2
	Mental state	2
Total number of items		49

Statistical Analysis

Demographics are presented using means and standard deviations (SD) as well as frequencies as appropriate. Ratings on SASNOS were transformed into a standard distribution, and T-scores were calculated using the SASNOS scoring program available online (32). Based on the standardized T-scores, number of ratings below T-score of 40 were calculated. Univariate analyses were applied to investigate associations between factors related to the patient, proxy, injury, and NBD. Furthermore, differences between patient's and proxy's scores were investigated using paired samples *t*-tests. All statistical analyses were conducted using SPSS version 22.0.

RESULTS

A total of 32 patients and 31 proxies completed and returned SASNOS. The majority of the patients were male (68.8%), and the majority of proxies were female (58.1%). Most proxies were spouses (51.6%) and parents (29.0%) living with the patient (61.3%) (**Table 2**).

Most brain injury survivors had suffered a traumatic brain injury (TBI; 68.8%) and had a mean age of 44.9 (SD 16.8) at time of the follow-up assessment. Most had sustained a severe injury indicated by length of PTA or period of confusion (**Table 3**).

The mean time since injury was 19.4 months (SD 10.0), and at time of follow-up, only a fourth of the patients were rated as having "good recovery" indicated by GOSE score of 7 or 8.

Neurobehavioral Disability Measured by SASNOS

Scores outside normal range: Raw scores on SASNOS were transformed to T-scores, and number of patients scoring outside the normal range were investigated. Based on the recommendations by the original authors, normal range was defined as more than 1 SD below the mean (5), and consequently a cut-off of T-score <40 was used (6). Number of patients rated below the cut-off were calculated (**Table 4**). Eight patients (25%) rated themselves as below cut-off on the Interpersonal Behavior

TABLE 2 | Demographic characteristics of patients and proxies.

Characteristics		Patient group (*n* = 32)	Proxies (*n* = 31)
		***n* (%)**	***n* (%)**
Gender	Male	22 (68.8)	13 (41.9)
	Female	10 (31.3)	18 (58.1)
Relationship	Spouse		15 (51.6)
	Parent		9 (29.0)
	Sibling		1 (3.2)
	Child		2 (6.5)
	Close friend		2 (6.5)
	Other type of relative		1 (3.2)
Cohabitants	Yes		19 (61.3)
	No		12 (38.7)

TABLE 3 | Patient characteristics.

Characteristics related to the injury		Patient group ($n = 32$)
		***n* (%)**
Etiology	TBI	22 (68.8)
	NTBI	10 (31.3)
	Anoxia	2 (6.2)
	Stroke	6 (19.2)
	Meningioma	2 (6.2)
		Mean (SD)
Age, time of injury		43.56 (16.92)
Age, follow-up		44.97 (16.80)
Length of PTA(TBI)/Confusion(NTBI) (days)		87.44 (88.02)
Time since injury at follow-up (months)		19.42 (10.02)
GOSE, at follow-up		5.72 (1.44)

TBI, traumatic brain injury; NTBI, non-traumatic brain injury; GOSE, Glasgow Outcome Scale Extended.

TABLE 4 | Number of patients below cut-off (*T*-score below 40) self-rated or rated by proxies.

	Patient rating ($n = 32$) *n* (%)	Proxy rating ($n = 31$) *n* (%)
Total sum rating	1 (3.1%)	1 (3.2%)
Interpersonal Behavior	8 (25.0%)	4 (12.9%)
Cognition	8 (25.0%)	10 (32.3%)
Aggression	1 (3.1%)	1 (3.2%)
Inhibition	0	0
Communication	1 (3.1%)	0

Number of patients rated with a T-score below 40, on self- or proxy-rating.

domain, whereas proxies only rated four patients (12.8%) below the cut-off on the same domain. On the Cognition domain, eight (25%) patients rated themselves below cut-off. On the corresponding rating completed by proxies, 10 patients (32.3%) were rated below the T-score cut-off of 40. On the Aggression, Inhibition and Communication domains, only a few patients were rated below the cut-off.

The highest frequencies of patients outside the normal range were found on two major domains of Interpersonal Behavior and Cognition. Ratings are depicted in **Figure 1**.

Factors Associated With NBD Ratings

Differences were found in relation to time since injury and cohabitant status. Proxies rated the patients' cognition as significantly lower ($p = 0.006$) the longer the time since injury. Furthermore, proxies living with the patient rated the patient's Interpersonal Behavior ($p = 0.036$) and Aggression (0.044) domains higher, indicating fewer problems, than proxies not living with the patient. Another finding was that there was a significant association between proxies' ratings on the Cognition domain and the patients' scores on GOSE ($p = 0.001$) **(Table 5)**. No differences were found in relation to gender.

Concordance Between Patients' and Proxies' Ratings on Each Domain and Subdomain

Differences between ratings completed by proxies and patients were investigated and significant differences were found, both on the Total Sum ($t = -2.17$, df = 30, $p = 0.040$) and on the following domains; Cognition ($t = 2.33$, df = 30, $p = 0.027$), Aggression ($t = -3.22$, df = 30, $p = 0.003$), and Communication ($t = -3.60$, df = 30, $p = 0.001$). The mean scores are depicted in **Figure 2**. In relation to the domains Aggression and Communication, proxies rated the patients significantly higher, indicating fewer disabilities, whereas the opposite pattern was found on the Cognition domain.

Several subdomains were scored significantly different by patients and proxies, and these are shown in **Table 6**.

On a number of subdomains, proxies gave significantly higher ratings; Engagement ($t = -2.09$, df = 30, $p = 0.046$), Irritability ($t = -2.93$, df = 30, $p = 0.007$), Overt aggression ($t = -2.38$, df = 30, $t = 0.024$), Speech and language ($t = -3.73$, df = 30, $p = 0.001$), and Mental state ($t = -2.09$, df = 30, $\boldsymbol{p =}$ 0.046). On the Executive functioning, patients gave significantly higher ratings than proxies ($t = 2.95$, df = 30, $p = 0.006$). These differences are depicted in **Figure 3**.

As shown in **Figure 3**, only on the Cognition subdomain, including Executive functioning, and Attention and memory, patients rated themselves higher, indicating fewer problems than considered by the proxies.

DISCUSSION

This study is the first to report results from the Danish version of SASNOS among proxies and patients with severe ABI. The aim of using SASNOS was to investigate NBD among severe brain injury survivors, factors associated with NBD, and differences between reports of NBD completed by survivors and proxies.

Frequency of NBD

The results of this study show how a fourth of this patient group reported themselves below the normal range on major domains of Interpersonal Behavior and Cognition. Proxies rated patients as having fewer problems of Interpersonal Behavior and more problems in Cognition. Both major domains have been shown to be sensitive when determining caseness, as they reflect the main problems experienced by ABI survivors. Ratings of symptoms on the remaining three domains Inhibition, Aggression and Communication, were more variable when compared to neurologically healthy adults (5). However, the reported frequencies below cut-off were lower than expected, specifically when considering that the patient group in the current study had suffered a severe ABI, as indicated by the length of confusional state or PTA. Compared to the results reported by Alderman et al. in 2011 and 2017, our patient group scored significantly higher, which indicates fewer problems (5, 6). This was the case for both the patient's self-rating, but also for the proxy ratings. However, a profound difference between

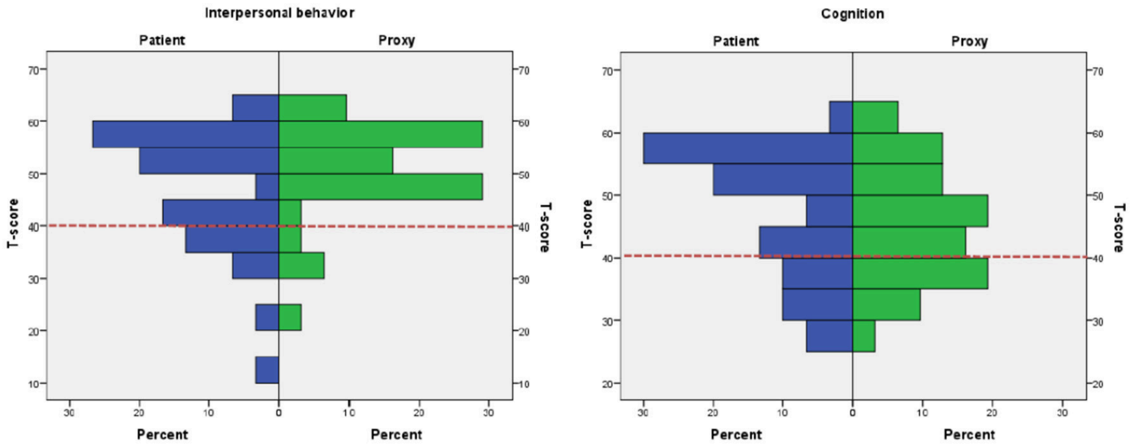

FIGURE 1 | Histograms depicting patient vs. proxy ratings on the major domains Interpersonal Behavior and Cognition. Proxy and patient ratings on Interpersonal Behavior and Cognition. Red dotted line indicates the cut-off of *T*-score 40.

TABLE 5 | SASNOS domains by proxy and patient characteristics.

SASNOS	**All** **Mean (SD)**	**Time since injury** **Mean (SD)**		**Cohabiting** **Mean (SD)**		**GOSE** **Mean (SD)**	
Main domain	Patient (*n* = 31) Proxy (*n* = 31)	12 mths (*n* = 18)	>12 mths (*n* = 13)	Yes (*n* = 19)	No (*n* = 12)	3–5 *n* = 11	6–8 *n* = 20
INTERPERSONAL BEHAVIOR							
Patient	46.42 (11.95)	46.6 (13.3)	47.0 (10.4)	46.5 (11.0)	46.3 (13.7)	45.2 (12.9)	47.7 (11.5)
Proxy	49.71 (9.59)	51.4 (10.4)	48.6 (8.2)	**53.0 (6.2)**	**45.8 (12.2)**[b]	47.5 (8.5)	51.5 (9.9)
COGNITION							
Patient	47.56 (10.70)	50.0 (10.7)	45.1 (10.2)	47.6 (11.0)	47.6 (10.8)	46.5 (11.3)	48.6 (10.4)
Proxy	44.36 (8.91)	**49.0 (8.7)**[a]	**40.1 (7.6)**	45.6 (10.1)	44.7 (8.3)	**38.0 (6.7)**	**48.7 (8.4)**[c]
INHIBITION							
Patient	61.70 (6.53)	62.8 (6.9)	60.4 (5.7)	63.0 (5.1)	59.7 (8.2)	59.9 (6.6)	62.8 (6.3)
Proxy	61.80 (6.12)	62.7 (6.5)	60.6 (5.6)	62.9 (5.0)	60.0 (7.5)	61.5 (4.3)	62.0 (6.9)
AGGRESSION							
Patient	62.34 (9.34)	63.3 (10.2)	61.6 (8.1)	64.6 (5.9)	59.0 (12.5)	59.7 (7.7)	64.2 (9.9)
Proxy	65.40 (7.25)	66.2 (7.5)	64.3 (5.9)	**67.4 (3.6)**	**62.2 (10.0)**[b]	65.5 (6.1)	65.4 (7.7)
COMMUNICATION							
Patient	56.32 (8.91)	58.3 (7.6)	53.9 (9.9)	58.4 (7.9)	53.2 (9.7)	54.1 (9.3)	57.7 (8.4)
Proxy	61.80 6.63)	63.0 (5.2)	60.3 (7.9)	62.4 (4)	61.0 (6.4)	63.3 (4.5)	61.2 (7.3)

[a]$p < 0. 01$ ($p = 0.006$); [b]$p < 0.05$ (Interpersonal behavior, $p = 0.036$); [b]$p < 0.05$ (Aggression $p = 0.044$); [c]$p < 0.001$ ($p = 0.001$). Significant differences are marked with bold. GOSE, Glasgow Outcome Scale Extended.

our study and the studies conducted by the original authors, is that the patient group in the original studies were rated by professionals working in the rehabilitation setting. It is more than likely that professionals might assess patients differently than a close family member, which served as proxies in our study. Furthermore, the Alderman studies were conducted, respectively 10.5 years (5) and 40.9 months after injury (6). Thus, these studies were completed at a much longer time since injury. Consequently, the patient groups are not completely comparable, which might partly explain the differences. Also, in our group, patients with the most significant NBDs might have been excluded, as they were not able to complete SASNOS independently.

Very recently, the original authors have proposed recalibrating NBD ratings to reflect context-depending support (18). This method would reflect the needed support in relation to each item, consequently in many cases this would assumably lower the obtained ratings.

Factors Associated With NBD Ratings

We found differences in relation to cohabitant status and NBD ratings. If the proxy and the patient lived together, the proxy tended to rate the patient as having fewer disabilities on the domains of Interpersonal Behavior and Aggression compared to proxies not cohabitating. This finding was in contrast to our expectations, as we expected that proxies in

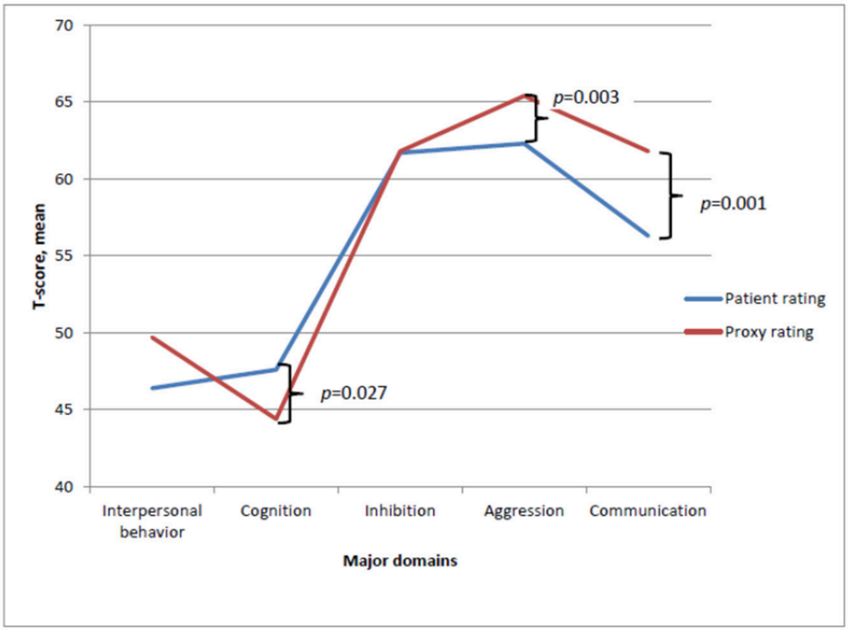

FIGURE 2 | Mean *T*-score ratings completed by patient and proxies on the major domains of SASNOS. Significant difference between patient and proxy ratings on the major domains Cognition, Aggression and Communication.

general would report more problems if they lived together, as they would experience the disabilities in activities of daily living first hand. A possible explanation could be a psychological defense mechanism preventing the proxy from acknowledging the disabilities. On the other hand, a proxy not living with the patient, will not have the opportunity to experience the progress in activities of daily living compared to a proxy cohabitating with the patient. One could speculate that this might be why non-cohabitating proxies report more problems. As far as the authors are aware, no studies have specifically investigated cohabitant status and its association with NBD self-reports.

Differences regarding time since injury were also found. Proxies reported significantly more problems on the Cognition domain, the longer time had elapsed since injury. A possible explanation might be the proxy's experience of hopelessness. Early in the rehabilitation process, the proxy may experience optimism in relation to change and spontaneous recovery but, as time goes by, they will have to adapt their life to accommodate the survivor's persisting pattern of disability (33). Contrary to our findings, a SASNOS study, where professionals completed the questionnaire, reported fewer disabilities the longer the time since injury. The largest change in scores was found on the Cognition domain (6). This challenges the belief that neurocognitive functions are static, and how spontaneous recovery might be seen for a longer period than expected (6). However, the design of the mentioned studies was very different with different follow-up periods, and comparative conclusions are difficult to make. Other studies also investigating NBD or neurobehavioral functioning after a brain injury, had fixed time intervals, ranging from discharge (25) to 1 year after injury (1). These fixed follow-up assessments also make it difficult to investigate associations related to time since injury.

Furthermore, we found a significant association between proxy's rating on the Cognition domain and the patient's score on GOSE, indicating more problems when lower GOSE score in obtained compared to a patient with a higher score. A similar association has been reported previously by Holm et al. (25) using the European Brain Injury Questionnaire (EBIQ) and the Glasgow Outcome Scale (GOS) score (25). These findings are not surprising, as lower GOSE scores indicate lower global outcome (28, 29).

Concordance Between Reports of NBD Completed by Survivors and Proxies

Significant differences were found between patient and proxy ratings. On both the Aggression and Communication domains, proxies rated patients higher, indicating fewer problems than rated by patients themselves. Cognition was the only domain where the patients rated themselves higher, meaning fewer problems compared with their proxies' rating which was in contrast to our expectations. Other studies investigating concordance between patients' and family members' ratings of disabilities have primarily used the Neurobehavioral Functioning Inventory (NFI), and most studies have been conducted in America. Despite differences between the SASNOS and NFI, some of the subscales are similar. NFI also investigates aggression, but where the present study found lower ratings for proxies than patients using SASNOS, Seel et al. found no significant differences on this scale (24). By comparison, Hart el al. found the opposite pattern, namely that proxies rated

TABLE 6 | Patient and proxy ratings on major and subdomains of the SASNOS.

SASNOS		Mean T-score (SD)	*t*-value	*p*-value
Total sum of ratings	**Patient**	**54.40 (8.70**	**−2.167**	***0.040***
	Proxy	**56.36 (7.29)**		
Interpersonal behavior	**Patient**	**46.42 (11.95)**	**−1.798**	**0.083**
	Proxy	**49.71 (9.59)**		
Social interaction	Patient	46.72 (8.67)	−0.655	0.517
	Proxy	47.87 (7.81)		
Relationships	Patient	45.65 (14.64)	− 1.974	0.058
	Proxy	49.87 (11.01)		
Engagement	Patient	49.32 (12.60)	− 2.090	*0.046*
	Proxy	52.46 (9.92)		
Cognition	**Patient**	**47.56 (10.70)**	**2.331**	***0.027***
	Proxy	**44.36 (8.91)**		
Executive functioning	Patient	49.24 (8.95)	2.953	*0.006*
	Proxy	45.02 (9.17)		
Attention and memory	Patient	46.65 (13.42)	0.407	0.687
	Proxy	45.88 (10.75)		
Inhibition	**Patient**	**61.70 (6.53)**	**−0.104**	**0.918**
	Proxy	**61.80 (6.12)**		
Sexual inhibition	Patient	63.28 (5.02)	− 0.863	0.395
	Proxy	64.00 (4.04)		
Social inhibition	Patient	57.00 (9.40)	0.385	0.703
	Proxy	56.43 (8.43)		
Aggression	**Patient**	**62.34 (9.34)**	**−3.217**	***0.003***
	Proxy	**65.40 (7.25)**		
Provocative behavior	Patient	62.93 (6.71)	− 1.923	0.064
	Proxy	64.39 (7.08)		
Irritability	Patient	56.22 (12.54)	− 2.927	*0.007*
	Proxy	61.14 (7.82)		
Overt aggression	Patient	63.31 (8.93)	− 2.378	*0.024*
	Proxy	65.62 (5.94)		
Communication	**Patient**	**56.32 (8.91)**	**−3.596**	***0.001***
	Proxy	**61.80 (6.63)**		
Speech and language	Patient	52.41 (10.86)	− 3.728	*0.001*
	Proxy	59.66 (7.89)		
Mental state	Patient	57.95 (7.89)	− 2.088	*0.046*
	Proxy	60.77 (6.34)		

Total sum ratings, domains and subdomain are given in the table. Major domains are marked with ***bold****. Significant differences between patient and proxy ratings are italized.*

more problems than patients (1). This might be due to differences in time since injury (1, 24). In the Hart study, only on the Aggression subscale a significant difference was reported between proxy and patient ratings (1). On the Communication scale, the Seel study found a significant difference between the ratings, where patients rated problems on this domain more frequently than proxies did (24). This is in concordance with our study, underlining how patients might perceive this to be a more serious problem than their family members. Another study used EBIQ to investigate complaints following brain injury. They reported no significant differences between patients' and proxies' reports in relation to communication (25).

Cognition was the only domain, where patients reported fewer problems than their proxies. In both the Hart and Seel studies, no significant discrepancies were found between reports on cognition (1, 24). However, the Holm study found a significant difference in relation to cognition, where proxies rated a significantly higher degree of problems than did patients (25). This probably reflects problems with self-awareness, which is often impaired after an acquired brain injury (9). For example, Ciurli et al. noted that poor self-awareness was associated with disabilities in executive functioning (8). Such disability can affect the ability to self-report, as low self-awareness, especially the ability to be aware of one's thoughts and mental state, affects the ability to recognize problems, process, and store information about the self (9). Therefore, lack of insight into one's own disabilities may explain how brain injury survivors sometimes under-report post-injury disabilities (19). As Oddy et al. reported, 40% of family members stated that survivors refused to admit any disabilities following the injury (34). However, discrepancies between survivor and proxy ratings might reflect factors other than decreased self-awareness. For instance, the survivor's communication skills might affect how they are able to communicate such information about disabilities. Furthermore, premorbid personality, relationship to proxy, and the need for compensation or benefits might affect the reports of survivors. As far as the authors are aware, no studies have specifically investigated factors influencing survivors' ability to communicate information about their NBDs. Therefore, it is of great importance to include proxy reports. However, the validity of proxy ratings cannot be guaranteed. Proxies' subjective reports and ratings can be biased and unreliable because of high level of stress associated with trying to cope with changes in their life situation (8), especially when the patient exhibits changes in personality. However, Norup and Mortensen did not find association between personality changes in patients and increased distress in proxies (35). Consequently, whilst patient and proxy reports rely on a subjective evaluation, the method is still of great value to capture cognitive inefficiency in real life situations (5, 19, 20).

It is important to address the long-term impact of NBD and be aware of potential changes in the pattern or degree of disabilities over time. It has become evident that brain injury survivors spend more time at home, have fewer friends and social contacts than prior to the injury (36). Changes in personality (35, 37), cognition and behavior (38, 39) contributes to social handicap. Social isolation can be a consequence of experiencing problems with social interaction (31, 40, 41). Furthermore, due to cognitive disabilities and problems with emotional recognition the survivors might find it difficult to understand why others get upset with them, which can lead to further withdrawal and isolation. This can affect the ability to reintegrate and participate in activities of daily living (42). These consequences emphasize the necessity of a systematic assessment of NBD.

Study Limitations and Future Perspectives

The present study has some limitations. First of all, it is based on a relatively small sample. Over a period of two years, 32 patients met the inclusion criteria and agreed to participate in the study. The patients included had been hospitalized for specialized neurorehabilitation in the sub-acute phase. A criterion for this type of rehabilitation is that the injury is severe, which was

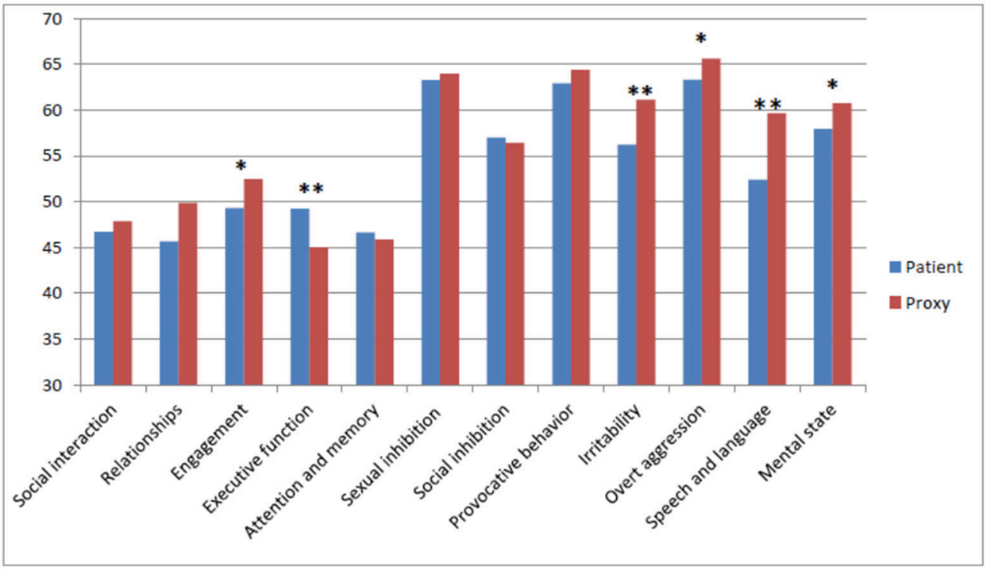

FIGURE 3 | Mean Scores on the subdomains as rated by patients and proxies. Level of significance: $^*p < 0.05$, $^{**}p < 0.05$.

supported by the patients' long period of confusion or PTA. This partly explains why it was not possible to include a larger number of participants. Some of the patients seen for the follow-up assessment in the outpatient clinic had severe cognitive disabilities, disorders of consciousness or severe aphasia. Patients with such disabilities were not able to complete the questionnaire and were consequently excluded. This affects the generalizability of the study, as patients with the most severe injuries might have been excluded. Using data from a cohort at a later stage post injury (> 2 years) could offer a larger sample size. Another reason for the small number of participants could also be a consequence of fatigue, which is common after ABI (43, 44). If a patient felt too exhausted to answer the questionnaire right after the follow-up assessment in the outpatient clinic, they were allowed to complete the questionnaire at home. However, in some cases they might have lacked the motivation to do so or forgot to return the questionnaire. We do not have any information concerning who completed the questionnaire at home or at the outpatient clinic. However, the participants were asked not to discuss their answers prior to completing and returning the questionnaires.

Second, the validity of patient ratings can be challenged if patients with severe brain injury lack the ability to recognize their disabilities. Furthermore, proxy ratings can be biased due to a high level of stress or emotional impact. However, SASNOS has shown good psychometric properties regarding reliability and validity and SASNOS is one way to measure NBD containing the subjective aspect of consequences after ABI.

Third, the single-center design is also a limitation, which warrants caution with respect to generalizing the results. However, as Department of Neurorehabilitation, TBI Unit, covers the Eastern part of Denmark that fact does expand the representativeness of the sample.

The use of SASNOS in this study has indicated areas of potential research. First of all, it could be interesting to explore the impact of the severity of injury in relation to concordance of reports on the SASNOS questionnaires. Second, it could also be of clinical interest to compare SASNOS profiles in cases who have or have not received rehabilitation after ABI. Third, a study exploring if a SASNOS profile at an early stage of recovery can predict psychosocial outcome at a later stage, e.g., 2 to 5 years after injury, would be of clinical interest. If it is possible to identify factors continuously influencing the patient's ability for community reintegration in long-term, it would be possible to focus early or medium-term clinical interventions to help the patient and the family adapt, accommodate, and minimize the social handicap consequent upon NBD. This would be a fruitful area for future research studies, from which both patients and their families would benefit.

AUTHOR CONTRIBUTIONS

All authors contributed to conception and design of the study; PS organized the database. AN performed the statistical analysis. PS and AN wrote the first draft of the manuscript. All authors wrote sections of the manuscript and contributed to manuscript revision, read and approved the submitted version.

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Vocational Rehabilitation in Mild Traumatic Brain Injury: Supporting Return to Work and Daily Life Functioning

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Persisting post-concussive symptoms are challenging to treat and may delay return-to-work (RTW). The aims of this study were to describe a multidisciplinary and holistic vocational rehabilitation (VR) program for individuals with mild traumatic brain injury (mTBI) and to explore course and predictors of employment outcome during VR. The VR program was described using the Standard Operating Procedures (SOPs) framework. Further, a retrospective, cohort study on individuals with mTBI receiving VR was conducted based on clinical records ($n = 32$; 22% males; mean age 43.2 years; 1.2 years since injury on average). The primary outcome was difference in hours at work per week from pre- to post-VR, and the secondary outcome was change in a three-level RTW-status. Time since injury, age, sex, and loss of consciousness were investigated as predictors of the outcomes. The VR intervention is individually tailored and targets patients' individual needs. Thus, it may combine a variety of methods based on a biopsychosocial theoretical model. During VR, hours at work, 17.0 ± 2.2, $p < 0.001$, and RTW-status, $\text{OR} = 14.0$, $p < 0.001$, improved significantly with 97% having returned to work after VR. Shorter length of time since injury and male sex were identified as predictors of a greater gain of working hours. Time since injury was the strongest predictor; double the time was associated with a reduction in effect by 4.2 ± 1.4 h after adjusting for working hours at start of VR. In sum, these results suggest that individuals facing persistent problems following mTBI may still improve employment outcomes and RTW after receiving this multidisciplinary and holistic VR intervention, even years after injury. While results are preliminary and subject to bias due to the lack of a control group, this study warrants further research into employment outcomes and VR following mTBI, including who may benefit the most from treatment.

Keywords: mild traumatic brain injury, concussion, post-concussive syndrome, vocational rehabilitation, multidisciplinary rehabilitation, return to work, employment, standard operating procedure (SOP)

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INTRODUCTION

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality worldwide and constitutes the third largest health expense in the USA (1, 2). The vast majority of cases (70–90%) are categorized as mild TBI (mTBI), or concussion (3). Individuals with mTBI tend to show considerable variation in post-concussive symptoms, which may include headache, fatigue, vestibular, and vision dysfunctions, increased sensitivity to light, noise, and pain, vertigo, sleep disturbances, cognitive deficits such as reduced concentration and poor memory, or mental health issues (4, 5). Most individuals sustaining mTBI recover spontaneously during the first week, however, a small subset continue to experience persisting symptoms beyond 3 months post-injury (6) with long-term implications for vocational, recreational, and social activities (7). Some individuals may even experience symptoms for more than 1 year after the incident (8). Persisting symptoms may delay return-to-work (RTW), reduce work productivity, adversely affect quality of life, and result in additional social and economic costs.

Evidence on vocational outcomes following mTBI is limited, and rates of RTW vary widely between studies (9, 10). Results of a systematic review suggest that most workers RTW within 3–6 months after mTBI, however, 5–20% continue to experience work limitations for 1–2 years post-injury (9), and possibly even longer (11). RTW is often associated with increased psychological well-being and quality of life (12), and is thus often identified as a major goal of recovery. However, even when returning to work, some individuals still experience distressing post-concussive symptoms, suffer from comorbid psychiatric conditions such as depression and anxiety, and work with functional limitations and reduced productivity (13). Further, individuals with mTBI may experience challenges maintaining employment over time.

Employment outcomes following mTBI can be complicated by multiple factors, including personal, injury-related, and environmental factors. Research regarding specific predictors of outcome such as age, sex, or various injury-related factors is mainly inconclusive (14). Some evidence suggests that a lower level of education, nausea or vomitting on hospital admission, extracranial injuries, severe pain early after injury, and limited job independence and decision-making latitude predict delayed RTW (9). Wäljas et al. (15) identified age, multiple bodily injuries, intracranial abnormality, and fatigue as predictors of delayed RTW, and Vikane et al. (16) reported psychological distress, global functioning post-injury, and being sick-listed 2 months after and the last year before mTBI as predictors. Looking more specifically at productivity loss, Silverberg et al. (13) found that residual symptoms and comorbid psychiatric conditions were predictors, and regarding long-term outcomes, Theadom et al. (11) reported that cognitive complaints at 1 month post-injury were predictive of work limitations 4 years post-injury. A recent systematic review supports the role of cognition in predicting and facilitating RTW (17). Thus, a range of factors, including demographic, physical, cognitive, and emotional as well as environmental and societal, may impact the course of employment outcomes after mTBI in a complex interaction, which is yet unclear.

Treatment of persistent symptoms after mTBI is based on limited evidence (18), and so is vocational rehabilitation (VR) more specifically (19). VR can broadly be defined as "whatever helps someone with a health problem to stay at, return to and remain in work" (20) and may require a combination of healthcare and workplace interventions. Regarding mTBI, there is clinical concensus that recommendations should be individually tailored and based on a multidisciplinary evaluation of personal, environmental, and occupational factors (21). Thus, VR constitutes a combination of individually tailored approaches; from initial assessment through intervention to evaluation of the patient's progress. Examples of means of promoting RTW and improving employment outcomes may be to reduce and in turn, if possible, gradually increase weekly working hours, to modify job demands, tasks, and the work environment, and to introduce rest breaks during the work day (19).

VR, like other interventions within rehabilitation, lacks definitions of treatment approaches. Definition and development of treatment manuals within neurorehabilitation have been debated comprehensively in the literature for more than a decade. However, there is still no clear-cut recipe or right or wrong way of how to develop an efficient treatment manual in this complex and multidisciplinary field of treatment, where interventions involve a variety of different methods. In designing a manual, one has to balance between how rigid vs. flexible, how long vs. short, and how detailed vs. broad to make the manual, all depending on the context, in which it is to be used, and the nature of the treatment itself (22–26).

Previous research has primarily investigated the course of RTW following mTBI, and only few studies investigated the course and predictors of more detailed employment outcomes in individuals with mTBI undergoing VR. Further, contents and strategies of VR for mTBI are seldom described in detail. This study aimed to describe a multidisciplinary and holistic VR program for individuals with persisting post-concussive symptoms. Further, the study aimed to compare employment outcomes in individuals with mTBI before and after completing the VR program. It was hypothesized that participants work more hours per week following the VR program. Finally, the study aimed to investigate a panel of four baseline characteristics as predictors of employment outcomes in an exploratory analysis. Apriory, time since injury was considered the most influencial factor, then secondary age, sex, and loss of consciousness in parallel.

MATERIALS AND METHODS

Design and Setting

This study was conducted at the specialized brain injury center BOMI in Denmark. BOMI offers multidisciplinary and individually tailored VR for individuals with brain injury, including mTBI and comorbid conditions. First, the Standard Operating Procedures (SOPs) framework was used to describe the VR program for mTBI. Second, a retrospective cohort study was conducted based on clinical records.

Development of Standard Operating Procedures

Aims, contents, and procedures for each module of the VR program were described in an intervention protocol using the SOPs framework (27). SOPs are specific standardized procedures that regulate the routine actions of individuals in specific positions and assign roles and responsibilities. SOPs within neurorehabilitation can act as a local adaptation of clinical guidelines (if such exists), based upon evidence-based practice. Implementation of guidelines in clinical practice often requires adaptation by the local workplace, where the guideline recommendations are combined with expert knowledge and routines. SOPs will help bridge the gap between evidence-based medicine (clinical guidelines) and the local circumstances and possibilities for carrying out rehabilitation. The SOP guides both the experienced and the inexperienced therapist through the same decision making processes to support a goal-oriented manner of practice.

For development of the SOPs, two representatives of each professional group in the multidisciplinary team providing VR at BOMI were recruited. That is, two occupational therapists, two physiotherapists, and two neuropsychologists. To be included, professionals had to be skilled with VR; hence, they had to have at least 2 years of experience with VR at BOMI. The staff members participated in workshops to discuss theory, goals, effective components, and practical approaches of VR.

Cohort Study

Participants

BOMI Center for Rehabilitation and Brain Injury receives individuals with acquired brain injury from a large number of Danish municipalities, primarily from the Capital and Zealand regions of Denmark. Since 2011, one municipality from the Capital region has consistently referred all individuals, who require treatment for persisting symptoms following mTBI, to receive multidisciplinary treatment and VR at BOMI. For this study, we included all individuals with an mTBI diagnosis from this municipality, who had received VR at BOMI between 2011 and 2018. Individuals are referred to BOMI as soon as they report problems that involve sick leave from work for more than 1 month or a need to take a sick leave after struggling with symptoms for several months. Consequently, time since injury may vary among referred individuals. Individuals have not necessarily been hospitalized for their mTBI. In the beginning of this collaboration, the municipality did not identify as many individuals with mTBI as in the later years. The identification procedures needed to be implemented throughout different levels in the organization of the municipality where moderate to severe TBI previously were prioritized. However, during the years, the procedures of how to identify individuals with persisting symptoms after mTBI became more clear and the number of referred individuals with mTBI increased.

Clinical records at BOMI were screened to confirm that participants of this study had been exposed to a trauma involving a direct blow to the head or involving a coup-contrecoup movement. Further, participants had to fulfill at least one of the following criteria: Loss of consciousness (max. 30 min), post-traumatic amnesia for a period of max. 24 hours, disturbance of consciousness (confusion or disorientation in time, place, or personal data), or transient neurological symptoms. In addition, participants had to have a Glasgow Coma Scale score above 13 after 30 min. All participants completed the planned rehabilitation program.

Measures

Data was collected from clinical records and chart reviews. Pre-injury data was self-reported retrospectively at start of VR.

Demographics and injury-related factors

Demographics were recorded, including sex, age, educational level, living arrangement, and number of children. The following injury-related data was recorded: Time since injury, the event causing injury, loss of consciousness at injury, and earlier incidents of concussion. Finally, duration of VR was recorded. The duration of VR depended on a variety of factors, including the patients' progress and needs and the financial frame granted by the municipality.

Employment outcomes

Four indicators of employment outcome were evaluated: Hours at work per week, RTW, full-time vs. part-time work, and employment status. The number of hours at work or education (high school, college, or university level) was recorded for three time points: At time of injury (T_1), at start of VR (T_2), and at completion of VR (T_3). RTW was evaluated at pre- (T_2) and post-VR (T_3). RTW was divided into complete and partial RTW by comparison with working hours at time of injury (T_1). That is, complete RTW corresponds to returning to the same (or an increased) amount of hours per week compared to pre-injury, and partial RTW corresponds to returning to a reduced amount of hours. Full-time work was defined as ≥ 30 productive hours per week and part-time as $0 < 30$. Finally, employment status was evaluated as competitive employment, supported employment, or sick leave.

Intervention

All participants received individually tailored, face-to-face, multidisciplinary VR. Details of the program are described in the Results section.

Analyses

Demographics, injury-related variables and employment outcomes were explored using descriptive statistics. The primary outcome was defined as the difference in working hours before and after VR. This outcome was evaluated by linear models. The secondary outcome was RTW with three levels (i.e., complete RTW, partial RTW, and no RTW) and was treated as an ordinal outcome. This outcome was evaluated by ordinal regression. For both outcomes, four variables were investigated as predictors: time since injury, age, sex, and loss of consciousness. They were investigated univariately using simple linear models with either categorical or continuous variables as predictors, reporting relevant effect sizes. Initial inspection of data revealed that the distribution of data for "time since injury" differed from being normally distributed, and this variable was hence log2 transformed before the main analyses. The statistical analyses were conducted in R version 3.4.2 (28) using describe() and stat.desc() from the packages psych and pastecs, respectively, for descriptive statistics, ggplot2 for plotting, base lm() and glm() for linear models and clm() from the ordinal package for ordinal regression. For mixed effect longitudinal models, lmer() from lme4 was used.

Ethics

The study was conducted in concordance with the Declaration of Helsinki, and the database was approved by the Danish Data Protection Agency (J.no. 2017-41-5256).

RESULTS

A Multidisciplinary Vocational Rehabilitation Program

In this section, the SOPs for VR of concussion are described in headings offering an overview of its content. The SOP theoretical foundation is based on a biopsychosocial theoretical model and the hypothesis that post-concussion symptoms probably represent the cumulative effect of multiple variables such as trauma severity, genetics, mental health history, current life stress, general medical problems, chronic pain, depression, social problems, and personality. Thus, a large variety of cause-effect interactions may contribute to the symptoms, and a full description is therefore not included in this paper.

The SOPs are nested in a circular process, aiming at a continuous evaluation of a patient's progress and responses to treatment. The therapist begins by setting goals for the patient based on an initial analysis of the patient's symptoms and a hypothesis on the underlying causes. Then the therapist chooses a strategy of how to reach the goals, by reanalyzing the patient's state according to goals and treatment. The therapist relates the choices of action according to the hypothesis of underlying causes to the patient's problems, and adjusts the goals and intervention according to the continuous observation.

The VR program for mTBI is individually tailored for each patient and consists of different modules that address the patient's symptoms. Each module has the overall purpose of supporting the patient's workability, either in a direct or more in-direct manner. The combination, length, and intensity of the modules are determined based on the patient's situation, goals for the intervention, and the financial frame granted by the municipality.

The purpose of the concussion VR intervention is:

1. To delineate a holistic understanding of the patient's functioning and disability, and the individual factors involved, including assessment of fatigue, sleep disorders, headache, cognitive difficulties, visual and balance problems, mental health and coping strategies.
2. Supporting that the patient achieves a balance between home life, family life, leisure life, and working life so the patient can participate in necessary and desirable activities and roles.
3. To support the improvement of individual workability, and to allow the patient to RTW as soon and at as many hours per week as possible.

Ad1: Assessment and Analysis

First step in the VR intervention is to set goals for the intervention process and patient progress. Typical goals may consist of: Increased insight into different aspects of brain injury and its implications, goals of handling fatigue, incorporation of positive everyday routines to increase energy level throughout the day and prioritize desirable activities, scheduling and planning activities, goals of how to handle cognitive difficulties, monitoring own progress, and reflection of achieved functions.

Throughout this process, therapists collaborate with a neuropsychologist in order to continuously adjust the strategies to each patient's individual cognitive and psychological state.

Ad2: Individually Tailored Intervention

Second step is to plan intervention by setting up a hypothesis of the desired change in patient's physical, cognitive, mental, and/or behavioral state in order to reach the goal based on previous evaluations. Thus, the treatment must be somehow broad in methodology to incorporate an approach matching each patient's needs, goals, and circumstances.

Most of the intervention involves change of behavior and adapting compensational strategies. These strategies contribute to teaching the patient to manage different symptoms and daily living in a more appropriate way and initiate a positive lifecycle. The choice of modules, including the length and intensity of modules, all depend on the patient's symptoms and response to intervention. Modules may include:

Energy management (EM)

The therapist supports the patient in testing and implementing strategies of how to change routines and amount of daily activities so the patient's energy level will remain stable throughout the day. EM is a personal process where the therapist acts as a facilitator and coach. This involves supporting the patient to set up realistic goals for the energy management process involving that the patient works with: Habits, routines and ways of thinking, life values, family roles and identity, how to interact with others, and more.

Specific approaches in EM may be: Small breaks, breaks at fixed time points, midday nap, ensuring a good night sleep by introducing good sleep hygiene, testing need for ball blanket, use of mindfulness techniques, relaxation techniques, analyzing eating habits and implementing a healthy diet, performing exercise, and achieving positive experiences.

The therapist continuously follows the patient's energy level throughout the day, to help the patient adjust working hours, activity planning, adjusting according to surroundings and other personal or environmental factors both at work and at home. The occupational therapist is in charge of the EM approach in close collaboration with the neuropsychologist.

Neuropsychological intervention

The focus of the neuropsychologist is psychoeducation, involving reflection on the patient's thinking patterns regarding new life circumstances, depreciation of the symptoms, and anxiety and depression management. The neuropsychologist conducts an assessment of the psychological status, including symptoms and severity of depression, post-traumatic stress disorder, and anxiety. Furthermore, an evaluation of subjective cognitive level of functioning is conducted using an interview. Based on the psychological evaluation, the patient is offered individually adapted psychotherapy consisting of 3–30 sessions in which the patient is informed about the psychological and cognitive level of functioning, the interrelations of cognitive and psychological functions, thinking and behavioral patterns, and emotional reactions. Different compensation strategies are discussed and developed. Furthermore, existential dilemmas regarding new life circumstances such as health anxiety, relations, being in the world with new physical circumstances, altered time and space, and financial concerns are addressed.

Visual and balance training

Another key component of concussion VR is visual and balance training. This training is provided by a team of optometrists and physical therapists. The training involves individualized sensory integration, vestibular and proprioceptive exercises in combination with binocularity, fixation, tracking, vergence, and eye-hand coordination (29). Typically, the patient receives 16–23 weekly sessions (or every other week), depending on the severity of symptoms and responses to the exercises. This training also involves instructions of how to implement exercises and symptom management strategies in everyday activities and work.

TABLE 1 | Characteristics of the cohort.

Variable	Statistic	Participants (*N* = 32)
DEMOGRAPHICS		
Age^a, years	*M* (*SD*)	43.2 (11.1)
Sex		
Male	*n* (%)	7 (22%)
Female	*n* (%)	25 (78%)
Educational level, years of education		
0 ≤ 10	*n* (%)	3
11–13	*n* (%)	4
>13	*n* (%)	25
Living arrangement		
Cohabiting	*n* (%)	19 (59%)
Living alone	*n* (%)	9 (28%)
Living with parents	*n* (%)	3 (9%)
Missing data	*n* (%)	1 (3%)
INJURY FACTORS		
Cause of injury		
Fall	*n* (%)	11 (34%)
Traffic accident	*n* (%)	11 (34%)
Sports-related/blow to head	*n* (%)	10 (31%)
Loss of consciousness		
No	*n* (%)	25 (78%)
Yes	*n* (%)	7 (22%)
Time since injury^a, days	*M* (*SD*)	418.66 (531.8)
	Mdn (*IQR*)	195 (237.3)
Time since injury after VR, days	*M* (*SD*)	785.81 (511.2)
	Mdn (*IQR*)	637.48 (206.5)
Earlier incidence of concussion		
No	*n* (%)	29 (91%)
Yes	*n* (%)	3 (9%)
TREATMENT FACTORS		
Duration of VR, days	*M* (*SD*)	367.16 (158.7)
	Mdn (*IQR*)	366 (218)

M, mean; Mdn, median; VR, vocational rehabilitation. ^{a}At start of VR.

Physiotherapy

This treatment focuses on dizziness, balance problems, neck problems, pain, and headache. The training is performed individually and is often supported by home-exercises. The principles revolve around graduated exercise training, e.g., focusing on vestibular rehabilitation, active treatment on cervical spine, dynamic stability, adjusted according to pain and progress. The training always involves instructions of how to implement exercises and training in everyday activities. If severe neck problems are suspected, the patient is referred to a physical therapist specialist with a certification in neck problems. Further, if vision problems are suspected, the patient is referred to neuro-optometrist for visual assessment followed by interdisciplinary visual and balance training.

Mindfulness

The approach of mindfulness at BOMI is primarily based on "Mindfulness Based Stress Reduction" and, in addition, is inspired by "Mindfulness Empathy and Cohesion." The purpose is to help the patient gain increased focus on sensitivity, indulgence, self-care, and awareness. As for the other modules, specific techniques are individually planned according to the needs of patients. Exercises may include "body scan," sitting and/or walking meditation, breathing exercises, and gentle yoga with mindfulness of movements and bodily sensations.

Ad3: Vocational Support

In VR, it is recommended that the patient start on a low amount of working hours and a minimum amount of tasks. Thus, the patient typically commences with a few hours at work a day, few days a week, and with a low complexity in work tasks.

There is a close monitoring process of the patient's symptoms, and adjustment of hours at work and work tasks, to ensure that the total work load matches each patient's condition and energy level at work and at home. The therapist will usually see the patient once a week in the beginning, depending on the complexity and patient needs, whilst the frequency and intensity of contact decreases over time. The therapist may also act as a safety net for the patient. Thus, the patient is encouraged to contact the therapist outside of scheduled sessions if needed. The therapist has the authority to contact other relevant personnel, if necessary.

The therapist visits the patient's workplace to analyze and assess compensational strategies and need of work place adjustments. The assessment consists of the combination of subjective information (what the therapist is told by the workplace) and objective information (what the therapist observes at the workplace), and is continuously revised during workplace meetings and during individual contact with the

TABLE 2 | Employment outcomes at time of injury, at start of VR, and after VR.

Variable	Statistic	Pre-injury (T_1)	Pre-VR (T_2)	Post-VR (T_3)
Hours at work per week	*M* (*SD*)	33.7 (10.0)	10.2 (10.4)	27.1 (10.8)
	Mdn (*IQR*)	37 (0.5)	9 (16.5)	30 (17.5)
RTW-STATUS				
Complete RTW	*n* (%)	–	2 (6%)	14 (44%)
Partial RTW	*n* (%)	–	18 (56%)	17 (53%)
No RTW	*n* (%)	–	12 (38%)	1 (3%)
WORKING TIME				
Full-time (≥30 h)	*n* (%)	29 (91%)	3 (9%)	18 (56%)
Part-time (1–29 h)	*n* (%)	1 (3%)	17 (53%)	13 (41%)
No work (0 h)	*n* (%)	2 (6%)	12 (38%)	1 (3%)
EMPLOYMENT STATUS				
Competitive employment	*n* (%)	30 (94%)	15 (47%)	21 (66%)
Supported employment	*n* (%)	0 (0%)	1 (3%)	8 (25%)
Sick leave	*n* (%)	0 (0%)	15 (47%)	1 (3%)
Other[a]	*n* (%)	2 (6%)	1 (3%)	2 (6%)

Complete RTW represents working the same (or an increased) amount of hours compared to pre-injury, partial RTW represents working fewer hours compared to pre-injury, and no RTW represents not working any hours per week. VR, vocational rehabilitation; M, mean; Mdn, median; RTW, return-to-work. [a]Other includes unemployment and non-competitive work/non-payed work trials.

patient. Relevant compensational strategies vary from patient to patient and depend on the patient's difficulties and resources. Compensational strategies involves support related to: When and how the patient should take breaks during work, how the patient compensates for difficulties in forming and maintaining an overview of work tasks, as well as planning different work tasks.

Based on the compensational strategy analysis, the therapist and the patient have reflective conversations in order to help patients evaluate their difficulties and resources. This involves discussions of the linkage between difficulties at the work place and the brain injury, how to use selected compensational strategies, the purpose of incorporating positive working routines and reflection on the individual goals.

Cohort Study

Characteristics of the Cohort

Thirty-two participants were included in the cohort. Mean age at start of VR was 43 years ($SD = 11$; range 18–65 years), and 78% of the participants were female. The majority of participants were living with a partner (59%), 28% were living alone, and 9% were living with parents. Most participants (77%) had children with a median amount of 2 ($\mathrm{IQR} = 1$).

Median number of days since injury was 195 ($IQR = 273$; range = 77–2,030) at start of VR. Duration of VR varied from 97 to 778 days with a median amount of 366 days ($IQR = 218$). Incidents of injury included a fall (34%), a traffic accident (34%), sports-related injuries and injuries due to a blow to the head (31%). The minority of participants had been unconscious following the incident (22%). Please see **Table 1** for an overview of participant characteristics and **Table 2** for an overview of employment outcomes at pre-injury, pre-VR, and post-VR, respectively.

Differences in Employment Outcomes Before and After Vocational Rehabilitation

From pre- to post-VR, mean hours at work per week increased significantly by 17.0 ± 2.2, $p < 0.001$. Each participant either remained or increased the amount of working hours from before to after VR (see **Figure 1**). That is, no participant worked fewer hours after VR.

In terms of RTW, the levels of RTW changed significantly, $\mathrm{OR} = 14.0$, 95% CI [3.5, 55.1], $p < 0.001$, from before to after VR (see **Figure 2**). Over the course of VR, no participant regressed in RTW-status (e.g., from complete RTW to partial RTW or from partial RTW to no RTW). On the contrary, RTW-status improved for 16 participants (50%) and remained stable for 16 participants (50%). As depicted in **Figure 2**, the difference in RTW-status was larger between no RTW and partial RTW, $p < 0.001$, than between partial RTW and complete RTW, $p < 0.51$.

Predictors of Outcome

Time since injury and sex were significant predictors of change in working hours during treatment (see **Table 3**). More specifically, double the time since injury was associated with a reduced gain of 5.8 ± 1.4 h, $p < 0.001$. That is, an individual receiving VR at day 100 since injury is observed having 5.8 more working hours per week from treatment compared to an individual receiving VR at day 200. However, participants starting VR in later phases of injury have more time to get back to more hours of work before starting VR, and may thus benefit less from VR, which could explain this association with time. Consequently, we introduced hours at start of VR as a covariate in the model, and the effect of time since injury attenuated from 5.8 to 4.2 ± 1.4, but remained significant, $p = 0.006$. Regarding sex, males had 11.2 ± 5.1 h better effect of treatment compared to women, $p = 0.035$. Age

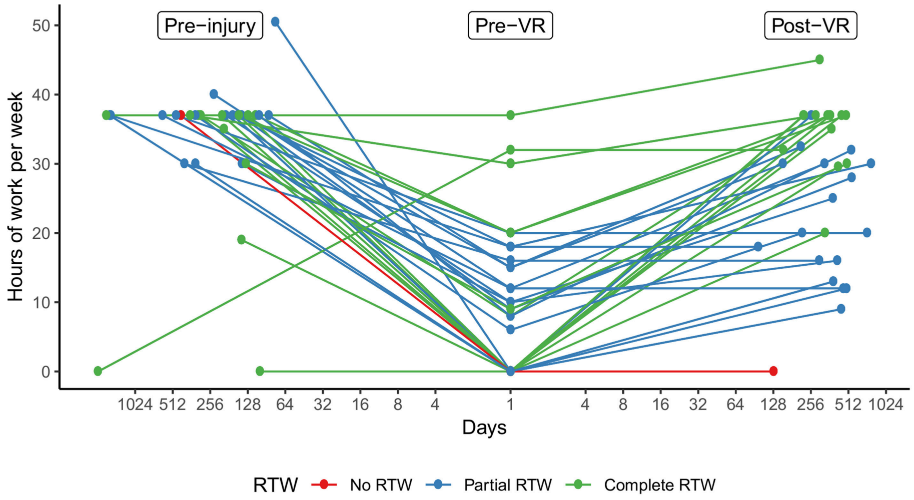

FIGURE 1 | Trajectories of hours at work per week. The graph illustrates each participants' amount of working hours per week on the y-axis at the time of injury (pre-injury; T_1), at start of VR (pre-VR; T_2), and after VR (post-VR; T_3). Time points are distributed on the x-axis by the number of days (log2 transformed) from injury to pre-VR and from pre- to post-VR. Colors indicate RTW-status at post-VR. VR, vocational rehabilitation; RTW, return-to-work.

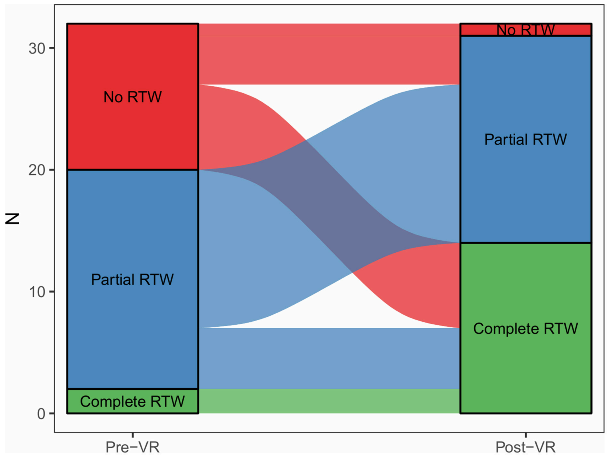

FIGURE 2 | Trajectories of return-to-work status. The graph illustrates participants' development in RTW-status from pre- to post-VR. Streams ending at a higher-level color (0 = red/no RTW; 1 = blue/partial RTW; 2 = green/complete RTW) represent improved RTW-status, streams ending at its own color represent stable RTW-status, and streams ending at a lower-level color would represent regressed RTW-status (no cases of this). Complete RTW represents working the same (or an increased) amount of hours compared to pre-injury, partial RTW represents working fewer hours compared to pre-injury, and no RTW represents not working any hours per week. RTW, return-to-work; VR, vocational rehabilitation.

and loss of consciousness were not significant predictors. In terms of RTW, similar but weaker effects of predictors were observed compared to hours at work.

DISCUSSION

This study described a holistic VR program for mTBI and found that individuals with mTBI had improved employment outcomes after completing the VR program. Time since injury and sex were statistically significant predictors of increase in working hours during treatment.

Developing a Vocational Rehabilitation Program Within Neurorehabilitation

The holistic approach of this VR intervention can be a complex treatment to learn and conduct, particularly for inexperienced therapists. Thus, a program based on SOPs can act as a tool guiding the clinical reasoning process, by describing the different ways to assess and treat symptoms and the hypothesis of the cause-effect interaction. Moreover, the SOPs will make it easier to disseminate the program to professionals.

The combination of interventions in a multidisciplinary VR program differentiates in nature from more focused interventions such as UPFRONT for mTBI, described by Scheenen et al. (30). UPFRONT is a short intervention involving five sessions of cognitive behavioral therapy aiming at facilitating RTW by enhancing the individual's feeling of competency. Such programs have a clear advantage of being more easily defined, and thereby more easily replicated and adjusted if needed. The Individual Placement and Support (IPS) model, used in other VR studies (31), is another manual-based VR intervention for individuals with brain injury. However, this method involves vocational support only and does not consider other aspects that might influence workability. Given the complexity of mTBI symptoms, it may be important to consider the interaction of biological, psychological, social, and environmental factors (32) in a VR program such as the one described here. LeBlanc and McLachlan (33) further support this view in a study that found an early individualized educational approach to be more effective for employment re-engagement than a general group-based intervention in a cohort of individuals with mTBI.

TABLE 3 | Predictors of difference in hours at work per week from pre- to post-VR.

	Hours at work				Model parameters		
Predictor	***n***	**range**	***M* (*SD*)**	***Mdn* (*IQR*)**	**Estimate (*SE*)**	***p***	**R^2[a]**
CATEGORICAL VARIABLES							
Sex							
Male	7	14–37	25.7 (10.2)	21 (18)	11.2 (5.1)	0.035	0.140
Female	25	0–37	14.5 (12.2)	13 (14)			
Loss of consciousness							
No	25	0–37	16.5 (12.8)	15 (14)	−2.3 (5.4)	0.682	0.006
Yes	7	0–37	18.7 (12.7)	17.5 (15.3)			
NUMERICAL VARIABLES							
Age[b], years					0.01 (0.21)	0.960	<0.001
Time since injury[b,c], days					−5.82 (1.40)	<0.001	0.364

Model parameters were estimated by simple linear regression. Response of the linear models was specified as the difference in hours at work from pre- to post-VR. M, mean; Mdn, median; VR, vocational rehabilitation. [a]For ordinal regression, this value represents the generalized R^2. [b]At start of VR. [c]Log2 transformed. i.e., the effect estimate reflects the change in hours by doubling of the predictor.

Vocational Rehabilitation and Employment Outcomes Following mTBI

During the course of VR, the cohort increased significantly in productive hours per week and improved in RTW-status. Following VR, 97% of participants had RTW compared to 63% before VR. Cancelliere et al. (9) estimated that about 5–20% of workers with mTBI face persisting problems with regard to RTW 1 to 2 years post-injury, and found that research on the prognosis of RTW beyond 2 years of injury is limited. A recent study of 245 adults at 4 years post-mTBI reported that 17.3% had exited the workforce or reduced their working hours compared to pre-injury (11). Another study reported that 59.1% of individuals with mTBI ($n = 110$) returned to work-related activity following a specialized post-mTBI intervention, which was initiated a median of 3.3 months post-injury (34). Comparisons with the present study are challenging, not least due to the variation in time since injury and other baseline characteristics. However, with an average of 2.2 years since injury at completion of VR, these preliminary results indicate that individuals receiving VR has the potential to RTW and improve workability, even 2 years after mTBI. Although not investigated quantitatively in this study, returning to work and resuming former work capabilities may have a substantial impact on the sense of well-being, social integration, and quality of life (12). Thus, further research is warranted on long-term employment outcomes and the effects of VR for mTBI.

Not all participants, who had RTW, returned to pre-injury levels of employment (full RTW). Further, although being a statistically significant change, only half the cohort improved their RTW-status. In some cases, it may be necessary to recommend a reduction in working hours in order to maintain employment and daily life functioning on the long term. In fact, our clinical experience is that returning to pre-injury levels of employment too soon may worsen symptoms and thus be a barrier for maintaining employment to some individuals. Furthermore, the recommendation of graded RTW has been supported in other patient groups (35).

Due to the heterogeneity and complexity of problems after mTBI, we suggest that an important element for outcome success may be the multidisciplinary, holistic, and flexible approach of this VR program, in which the specific contents, intensity and length of the intervention is continuously adjusted to the individual needs of patients. However, this approach makes the program less easily defined and harder to replicate compared to more focused programs such as UPFRONT (30). Thus, a goal for future research could be to investigate the significance of flexibility in VR programs for outcome success after mTBI.

Predictors of Employment Outcome

First, results indicated that those starting VR earlier after injury gained more working hours during VR, even when adjusting for working hours at start of VR. There could be several plausible explanations to this relationship. For instance, "the sooner the better" could be a rule with regard to treatment effect or, alternatively, those starting VR later could have more severe or entrenched problems than those starting earlier and thereby benefit less from treatment. How to interpret this relationship is not evident from this study and would possibly require research involving dubious ethical protocols.

Second, we found that men improved significantly more in working hours than women. The reasons for this relationship are unclear, and the results are in conflict with a systematic review finding that sex did not predict RTW following mTBI (9). However, previous research has suggested that women report more post-concussive symptoms than men, although this finding is not consistent (36, 37). Given that women experience more symptoms, e.g., mental health issues such as depression and stress, this could influence RTW and explain why VR was less beneficial for women compared to men in this study. However, we did not have indicators of symptom severity, and further research is needed to provide insight into this matter.

Generalizability

Since all individuals included in the study were recruited from a single municipality, it is relevant to consider potential biases related to demographics. The included municipality is characterized by a relatively high average income with 55.7% of the population having a higher income than the country's average, and the citizens are highly educated compared to the national average. Thus, the recruitment design of this study introduces a risk of selection bias, and demographics could be influencing the results positively. Further studies would have to investigate whether this VR design applies to individuals from other municipalities with work and education levels closer to and below the country's average.

LIMITATIONS

This study had several limitations. First, the study design was retrospective in nature, the cohort was relatively small, and we did not have a control group. Although results are promising, they are preliminary and do not allow for specific inferences regarding effect of intervention. Although, we adjusted for working hours at start of VR in predictor analyses, the effect of time since injury could reflect spontaneous recovery, and not necessarily a more beneficial effect of VR, in earlier phases of injury compared to later. Second, the cohort was a selected group of individuals with mTBI from one minor community in Denmark. Thus, results should be interpreted with respect to these selection procedures and the fact that results may differ for another population referred to VR under different circumstances. Third, we did not investigate whether participants were able to maintain employment beyond VR. Fourth, no data was available on amount and severity of symptoms.

CONCLUSION

In this study, we have initiated the work of defining a multidisciplinary and holistic VR program for individuals suffering from post-concussive symptoms using the SOPs framework. This program will be updated on an ongoing basis in line with its use in clinical practice; however, defining interventions in rehabilitation is an important step toward evidence-based practice and standardized methods. While results of this study are preliminary, both working hours and RTW-status improved significantly with 97% having RTW following VR. Time since injury and male sex were identified as predictors of outcome. In particular, double the time since injury was associated with a reduction of 4.2 h per week. Overall, these results suggest that individuals with persistent post-concussive symptoms may still improve employment outcomes, even years after mTBI. However, further research is needed for any firm conclusions to be drawn regarding the effect of VR, including predictors of effect.

AUTHOR CONTRIBUTIONS

FD wrote the first draft of the paper, organized data, performed descriptive analyses, and finalized the paper. TS conceived most part of the data, initiated the study, and had the primary role in describing the content of intervention in the results and discussion sections. MR discussed statistical methods, performed a substantial part of the data analysis, and contributed to description of the methods and results sections. LS is part of the research group and contributed with literature review and supported writing the final manuscript. EF is part of the research group and contributed with discussing the research design and population group, and with writing the manuscript. All authors critically read, improved, and approved the final manuscript.

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A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury

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Background and aims: Severe traumatic brain injury is a leading cause of acquired persistent disabilities, and represents an important health and economic burden. However, the determinants of long-term outcome have rarely been systematically studied in a prospective longitudinal study of a homogeneous group of patients suffering exclusively from severe TBI

Methods: Prospective observational study of an inception cohort of adult patients with severe traumatic brain injury in the Parisian area (PariS-TBI). Outcome was assessed with face-to-face interview 8 years after Traumatic Brain Injury, focusing on impairments, activity limitations, and participation restriction.

Results: Five hundred and four patients were included between 2005 and 2007. At 8-year follow-up, 261 patients were deceased, 128 were lost to follow-up, 22 refused to participate, and 86 were finally evaluated. Age, gender, initial injury severity did not significantly differ between evaluated patients and lost to follow-up, but the latter were more frequently students or unemployed. Mean age was 41.9 (*SD* 13.6), 79% were male, median initial Glasgow Coma Scale Score was 6. The most frequent somatic complaints concerned balance (47.5%), motricity (31%), and headaches (36%), but these were less frequent than cognitive complaints (Memory 71%, Slowness 68%, Concentration 67%). According to the Hospital Anxiety and Depression Scale (HADS), 25 % had a score >8 for anxiety and 23.7% for depression. According to the Extended Glasgow Outcome Scale, 19.8% remained severely disabled, 46.5% moderately disabled, 33.7% had a good recovery. Older age, longer education duration, lower functional status upon intensive care discharge, and more severe 8-year dysexecutive problems were significantly associated with a lower Extended Glasgow Outcome Scale score in multivariable analysis. At 8 years, 48.7% of patients were employed in a productive job. Of those, 38% declared a salary loss since traumatic brain injury. Unemployment was significantly associated with lower 1-year GOSE score and more severe 8-year dysexecutive problems.

Conclusions: These results from an inception cohort study highlight the fact that long-term outcome after severe TBI is determined by a complex combination of injury-related, demographic and neuropsychological factors. Long after the injury, persisting impairments still interfere with social integration, and participation.

Keywords: traumatic brain injury, outcome, longitudinal study, adult, independence, return to work

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of persistent disability worldwide. The likelihood of suffering disability increases with severity of TBI. In European countries, an overall incidence of 262 hospitalizations/100,000 inhabitants per year was derived from a meta-analysis (1). About 10% of TBI are considered as severe. The weighted average mortality for severe traumatic brain injury was 39%, and for an unfavorable outcome on the Glasgow Outcome Scale was 60% according to a 2012 meta-analysis (2). TBI often occurs in young adults who will live decades with a variety of cognitive, emotional, physical and sensory disabilities (3). Participation limitations have been described in numerous studies focusing on TBI outcome (4). In the majority of previous studies, outcome, and prognostic factors were assessed within the first 5 years after TBI (5, 6). It is admitted that the major part of the functional improvement is made in the first year (7, 8). However, some studies found a long-term improvement of independence or a relative stability (3, 9). These studies included patients from rehabilitation centers and might not be representative samples of all TBI patients as previous research found that severe TBI patients were not systematically referred to in-patient rehabilitation units (10, 11). Other studies, described the longitudinal outcome of severe TBI patients included since acute care but with relatively small samples (12, 13). Hence, there is a lack of knowledge about the long-term outcome (after 5 years) in homogeneous, consecutively admitted from acute care, and exclusively severe TBI patients.

Previous studies have shown that long-term outcome in term of global functioning of participation in a paid productive activity was determined by multiple factors, some of which were socio-demographic, such as age and sex, others were related to the severity of TBI (4, 6). The aim of the present study was to give a comprehensive picture of long-term (8-year) outcome in an homogeneous sample of patients with severe TBI and to assess its determinants or related factors, in line with the previous reports on this cohort (11, 14–19).

MATERIALS AND METHODS

Participants, PariS-TBI Study

Adults (aged more than 15 years) with severe traumatic brain injury (Glasgow Coma Scale score ≤8 before the hospital admission in absence of other cause of coma) in the Parisian area were recruited consecutively by mobile emergency services from 2005 to 2007 (20). A total of 504 patients were included. Main causes of injury were road traffic accidents (52%) and falls (34%). Pre-injury characteristics including gender, age, education duration, professional status as well as a history of alcohol abuse were documented from medical records and from information provided by relatives. The initial assessment included an assessment of disability at the intensive care unit (ICU) discharge with the Glasgow Outcome Scale (GOS) (21). Patients were followed-up at one, 4 and 8 years post-injury. The 1-year assessment was undertaken by a trained neuropsychologist by telephone interview with patients and their relatives. Four and Eight year outcome were documented by a face to face interview conducted by trained neuropsychologists with patients and their relatives. During the one, 4 and 8 year evaluations, a standardized questionnaire was used and various data were collected about home situation, marital status, work or study status, functional status, disabilities, and complaints. Inclusion criteria at the acute stage and data on 1 and 4-year outcome of the PariS-TBI study have been extensively reported in previous publications (11, 14–18, 22, 23). In the present study, we focused on patients who were evaluated at 8 years post-TBI.

There were 86 patients who attended 8-year follow-up, 268 patients were deceased (247 during the acute stage), 128 patients were lost to follow-up and 22 refused to participate. Sixty-eight (79%) out of the 86 evaluated patients were men, with a mean age at the time of TBI of 34 years (standard deviation [SD], 13.7), mean age at the time of evaluation of 41.9 years (*SD*, 13.6) and mean education duration 12.2 years (*SD*, 3.2). The initial Glasgow Coma Scale (GCS) score was three or four for 25.9% of the sample, five or six for 34.1%, seven or eight for 40%. The mean time to follow command was 12.4 days (SD, 10.6) and the mean length of stay in the intensive care unit was 28.8 days (SD, 23.8). The mean time since injury was 98.5 months (SD, 8.65). Four of the 86 patients refused to complete the totality of the questionnaire. Regarding return to work assessment, patients who were retired at the time of TBI or over 64 years old at 8 years were excluded resulting in a 76 patients sample.

Assessment

At 8 years post-TBI, a clinical evaluation and the standardized questionnaire assessed the independence in simple and complex daily living activities. For the study, we created a questionnaire to assess the neurological and somatic impairments. Patients were asked the following question "What are the physical difficulties you have because of head trauma?." Eleven of the most frequent deficiencies reported in previous studies were proposed with the possibility of classifying them as "none," "moderate," "severe." Cognitive and behavioral complaints were investigated with the Brain Injury Complaint Questionnaire (BICoQ), after the following explanation "We will ask you questions about the problems you face in your everyday life since the TBI." Twenty-five closed questions were given addressing frequently reported cognitive and behavioral complaints (19, 24). The same questions were asked to their relatives. Patients were asked about the recurrence of TBI and whether they suffered epilepsy or not.

The structured interview was developed for the study to assess impairments, activities, and participation according to the International Classification of Functioning, Disability, and Health framework (25). The global outcome was evaluated with the French version of the Glasgow Outcome Scale-Extended (GOSE) (20, 26). This frequently used rate scale allows classifying people in eight categories ranging from death to upper good recovery.

The Dysexecutive Questionnaire (DEX) was completed by the patient and their relative to assess executive dysfunctions in daily life (27). This is a 20-item questionnaire covering four broad areas of likely changes: emotional or personality changes, motivational changes, behavioral changes and cognitive changes. Each item is scored on a five-point (0–4) Likert scale (ranging from never to very often). The DEX is a multidetermined sensitive questionnaire to detect everyday life difficulties in patients with severe TBI at a chronic stage (23). Mood impairments were measured by the Hospital Anxiety and Depression Scale (HADS) (28), which has two subscores, for anxiety and depression, both ranging from 0 to 21 (highest anxiety or depression).

Patients were asked about the continuation or resumption of studies after TBI and working situation. Post-TBI difficulties at work were explored by a dedicated questionnaire which was developed by a group of experts and routinely used in a vocational rehabilitation unit. Self-perception and the consequences of the difficulties were assessed by the questionnaire and the responses, concerning twenty-two difficulties at work, were binary. Patients were then asked to assess the frequency and intensity of their difficulties at work on a four-point scale. Finally, patients were asked to estimate their perceptions of their peer's consciousness and tolerance of their difficulties at work, on a scale from zero to ten.

Ethics Approval Statement

In accordance with French legislation, patients and their relatives were informed about their initial inclusion in the database. Informed written consent from participants (or their legal representatives) was obtained before each study assessment. Furthermore, before the assessments at each study stage, approval was granted from Commissions which enforce research database legislation in France, and the local Ethical Committee (Comité de Protection des Personnes, CPP XI). The study was recorded in the ClinicalTrials.gov database in January 2014 (identifier: NCT02050633).

Statistical Analysis

Preinjury sociodemographic factors, injury-related factors, post-injury factors were described using means, standard deviations, minima and maxima for continuous variables. Median and interquartile range were used to describe numerical variables in small samples. Categorical variables were described using counts and percentages. Data were sometimes incomplete because some individuals did not provide answers to all questionnaires. In case of missing data, percentages were based on the number of subjects who answered the given questionnaire.

For univariate comparisons between employed and unemployed subjects at 8 years, we used a two-sided statistical analysis and a 5% significance level. Student's *t*-tests were used for continuous variables, Chi2 tests were used for categorical variables. When Chi2 results showed a dependent relation between the studied variables, the adjusted standardized residuals were calculated to assess the statically significant differences among cells of the contingency table (29, 30). For univariate analysis of 8-year GOSE score, an ordinal regression with cumulative link model was computed with each independent variable if proportionality assumption of the odds was met and a Spearman's correlation was calculated if not. Because of multiple comparisons in univariate analysis of GOSE and return to work related factors and associated type I error inflation, results were given with both *p*-values and corrected *p*-values according to Holm (31). For multivariable analysis of 8-years GOSE score, an ordinal regression with cumulative link model was computed and proportionality assumption of the odds was verified. We computed a two-step analysis with a first model including sociodemographic and injury-related variable and a second model including sociodemographic, injury related and post-injury factors. Independent variables were chosen if they were statistically significant in the univariate analysis. Although non-significant in the univariable analysis, age was kept in the multivariable analysis because previous studies found an important association between older age and poor functional outcome (4). For the first model, a stepwise selection of independent variable was made starting with the full model and iteratively removing the least contributive predictors, and stopping when having a model where all predictors were statistically significant. In the second model, although statistically significant in the univariate analysis, HADS depression and total scores were not included because the proportional odds assumption was not met for these variables.

RESULTS

Comparison Between Evaluated Patients and Lost to Follow up or Refusal to Participate

The univariate analysis of the comparison between evaluated patients and lost to follow up or refusal to participate is presented in **Table 1**. Evaluated and non-evaluated patients

TABLE 1 | Univariate comparison of evaluated and non-evaluated patients.

	Non-evaluated $n = 150$		**Evaluated $n = 86$**	**Missing data**	**p (chi^2) or p (student)**	**Corrected***
Patient characteristics	**Mean ± SD [minimum; maximum] or count (%)**	**Missing data**	**Mean ± SD [minimum; maximum] or count (%)**			**p (chi^2) or p (student)**
Gender		0 (0%)		0 (0%)	0.801	1
Female	28 (18.7%)		18 (20.9%)			
Male	122 (81.3%)		68 (79.1%)			
Age at time of TBI (years)	33.5 ± 15.9 [15.2–82.7]	2 (1.3 %)	34.1 ± 13.7 [15.4–74.8]	0 (0 %)	0.753	1
Education duration (years)	11 ± 2.6[5-18]	58 (38.7 %)	12.2 ± 3.2 [6-20]	8 (9.3 %)	0.008	0.099
Occupational class		32 (21.3%)		4 (4.7%)	<0.001	0.001
Blue collar	52 (44.1%)		33 (40.2%)			
White collar	5 (4.2%)		22 (26.8%)			
Retired	11 (9.3%)		4 (4.9%)			
Student	30 (25.4%)		17 (20.7%)			
Unemployed	20 (16.9%)		6 (7.3%)			
Employment preinjury		32 (21.3%)		4 (4.7%)	0.006	0.115
Yes	68 (57.6%)		59 (72%)			
No	50 (42.4%)		20 (24.4%)			
Living alone before TBI		4 (2.7%)		0 (0%)	0.257	1
No	113 (77.4%)		60 (69.8%)			
Yes	33 (22.6%)		26 (30.2%)			
Alcohol addiction before TBI		10 (6.7%)		5 (5.8%)	0.309	1
No	118 (84.3%)		73 (90.1%)			
Yes	22 (15.7%)		8 (9.9%)			
Initial GCS		7 (4.7%)		1 (1.2%)	0.942	1
3–4	36 (25.2%)		22 (25.9%)			
5–6	52 (36.4%)		29 (34.1%)			
7–8	55 (38.5%)		34 (40%)			
Duration of coma (days)	8.8 ± 7.7 [0–50]	18 (12 %)	9.6 ± 6.2 [0–24]	15 (17.4 %)	0.406	1
Time to follow command (days)	11.8 ± 11.9 [0–81]	22 (14.7 %)	12.4 ± 10.6 [0–56]	20 (23.3 %)	0.737	1
Length of stay in ICU (days)	24.6 ± 19.7 [2-134]	1 (0.7 %)	28.8 ± 23.8 [2–131]	0 (0 %)	0.171	1
GOS at ICU discharge	3.8 ± 0.9 [2–5]	20 (13.3 %)	3.8 ± 0.8 [2–5]	12 (14 %)	0.857	1

GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; GOS, Glasgow Outcome Scale.
**Corrected p-value according to Holm.*

were statistically significantly different regarding preinjury occupational level (Chi^2 $= 23.637$, df $= 4$, p-value < 0.001). Adjusted standardized residuals were only $> \pm 2$ for the "white collar" occupational class. White collar patients were significantly overrepresented amongst evaluated patients. There were no other between-group differences (particularly initial injury severity was not significantly different in the two groups). There was a trend for unevaluated patients to have shorter education duration and to be unemployed before TBI without Holm p-value correction.

Impairments, Activity Limitations, Global Outcome, and Living Situation

The frequency of somatic and neurological complaints of the 80 patients who completed the questionnaire is shown in **Figure 1**. The three most frequent somatic and neurological complaints were balance, motricity and headaches. Taste and smell complaints were the most frequently reported as severe by 17.5% of the sample. The sample had three somatic or neurological complaints at mean (*SD*, 2.2) and 15% did not have any complaint at all. The number of somatic or neurological complaint per subject is shown in **Figure 2**. The frequency of cognitive and behavioral complaints of the 76 patients who completed the questionnaire is shown in **Figure 3**. Eight complaints were reported by more than a half of the sample: noise intolerance (51.3%), need peace and quiet (55.3%), irritability (57. 9%), fatigue (60.5%), dual-tasking (64.5%), concentration (67.1%), slowness (68.4%), memory failures (71.1%). The mean number of cognitive and behavioral complaints was 10.4 (*SD*, 6.2) and only 7.9% of the sample reported none of the 25 complaints of the questionnaire. The number of complaints per subjects is shown in **Figure 4**.

None of the patients suffered another TBI in 8 years. Nine patients out of 82 (11%) declared having suffered seizure since TBI but only one had seizures during the past year.

Mean HADS scores were 6.2 (*SD*, 4.6) for anxiety and 5.5 (*SD*, 4.6) for depression. According to the previously defined cut-off

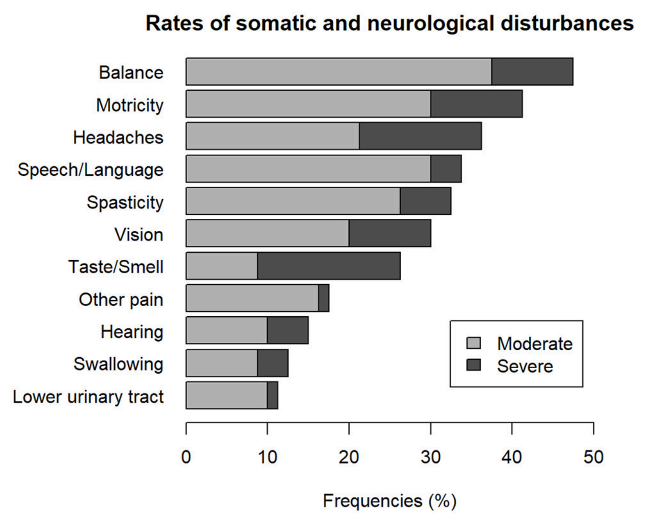

FIGURE 1 | Frequency of somatic and neurological complaints.

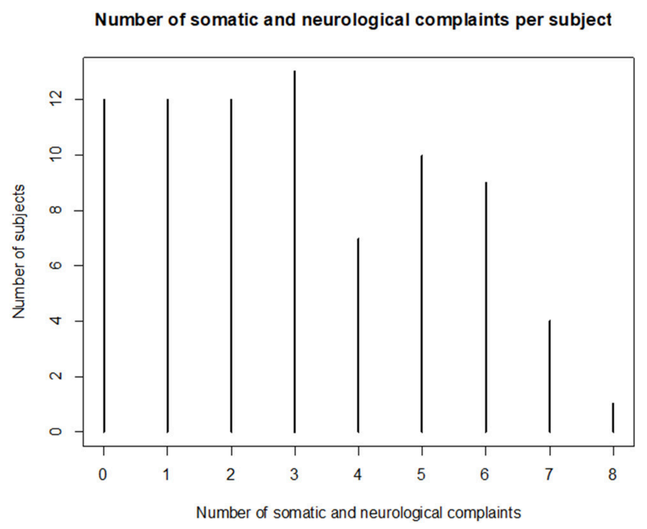

FIGURE 2 | Number of somatic and neurological complaints per subject 8 years after severe traumatic brain injury.

score of 8 points for these subscales, 8 subjects (10.5%) had an anxiety disorder and 7 (9.2%) had depression, 11 (14.5%) had both anxiety disorder and depression.

Global outcome based on GOSE scores is shown in **Figure 5**. The majority of patients (37%) fell in the upper Moderate Disability category.

Univariate analysis of variable associated with GOSE score at 8 years is shown in **Table 2**. A longer education, a shorter length of stay in intensive care unit, a higher GOS score upon intensive care discharge, a higher GOSE score at 1 year were associated with better outcome (i.e., a higher 8-year GOSE score). HADS depression and total scores as well as DEX total scores rated by patients or relatives were significantly higher amongst subjects with lower GOSE score after correction of the *p*-value according to Holm. There was a trend for higher initial GCS score to be associated with higher GOSE score at 8 years before *p*-value correction. On multivariable analysis (**Table 3**), the first model including sociodemographic and injury-related factors revealed that older age, shorter education duration, longer length of stay in ICU and lower GOS score at ICU discharge were associated with poorer global outcome. The initial GCS score was not kept by the stepwise selection. All variables of the first model except length of stay in ICU were still significantly associated with GOSE score after adding DEX score rated by patients. A lower DEX score was associated with a poorer global outcome.

The majority of subjects (90.2%) declared to be independent for dressing, grooming, moving inside the home, using the bathroom, 79.3% for taking public transport, 67.1% for writing a letter, 50% for financial and administrative management. **Figure 6** shows subjects independence or need for support in these activities. Most of the patients (51.2%) declared to be able to drive without limitation, 12.2% only on short distances travels, 36.6% did not drive motor vehicles. Only 40.4% of the subjects who resumed driving revalidated their driving license with an approved practitioner for capacity for driving.

Nearly half of the patients (49.4%) were in a relationship, 22.9% had children at home, 3.6% were single with children at home. Most of the patients (77.1%) declared living in their own home, 18.1% lived in a relative's home, 3.6% were living in an institution, one (1.2%) was still hospitalized since the TBI. Home Accessibility Modifications were made for 16.9% of patients and they all received funding to make the modification.

Education and Work

Six out of the 17 students at the time of the injury continued their education. These six patients had a job at 8-year follow-up. Of the 11 students who did not continue education, seven did not work at 8 years.

Eight years after the injury, 37 subjects (45.1% of the 82 evaluated patients and 48.7% of patients aged under 65) had a job. Only one patient worked in a sheltered workshop. Seventeen patients (41.5% of workers), declared that their job changed after TBI. This job modification corresponded to an occupational reclassification for 10 subjects (58.8%) and to a modification of tasks in the same kind of job for seven (41.2%). Twelve patients (70.6%) had changed employer. In comparison to pre-injury, among the 37 employed patients, nine (24.3%) decreased their working time, 25 (67.6%) remained the same and 3 (8.1%) increased their working time. Incomes had decreased for 14 subjects (37.8%), had remained stable for 19 (51.4%) and increased for 4 (10.8%). Regarding their responsibilities at work, two subjects (5.4%) declared an increase, 29 (78.4%) had not reported a change, 6 (16.2%) declared a decrease. Most of the patients (n=27, 73%) worked 80% to full time, eight (21.6%) worked half time to 79%, two (5.4%) worked less than half-time. Twenty-six subjects declared to plan a career development in the future. On average, subjects resumed work 27.8 months (*SD*, 27) after TBI. Seventeen patients (45.9%) followed vocational

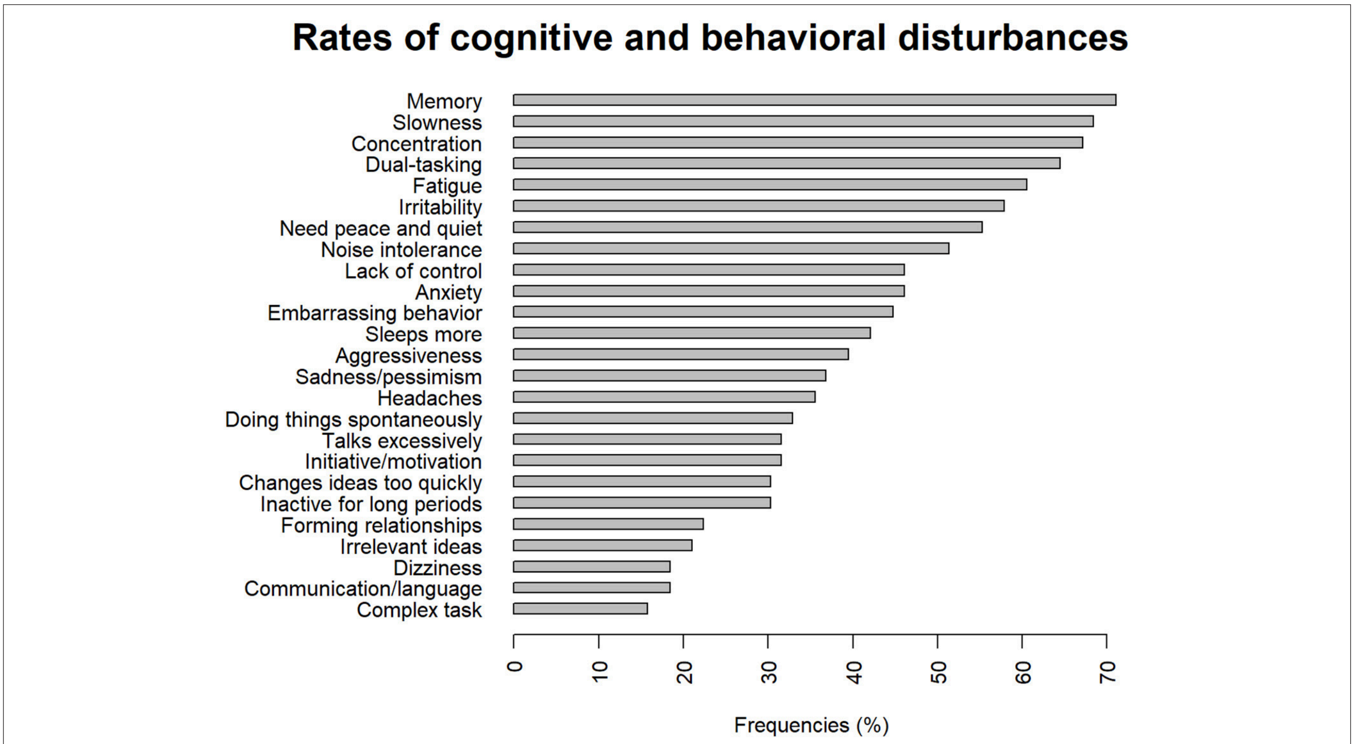

FIGURE 3 | Frequencies of cognitive and behavioral disturbances 8 years after severe Traumatic Brain Injury.

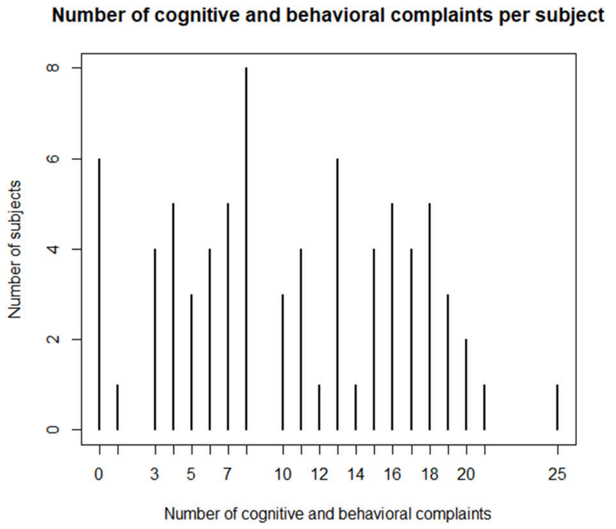

FIGURE 4 | Number of somatic and behavioral complaints 8 years after severe Traumatic Brain Injury.

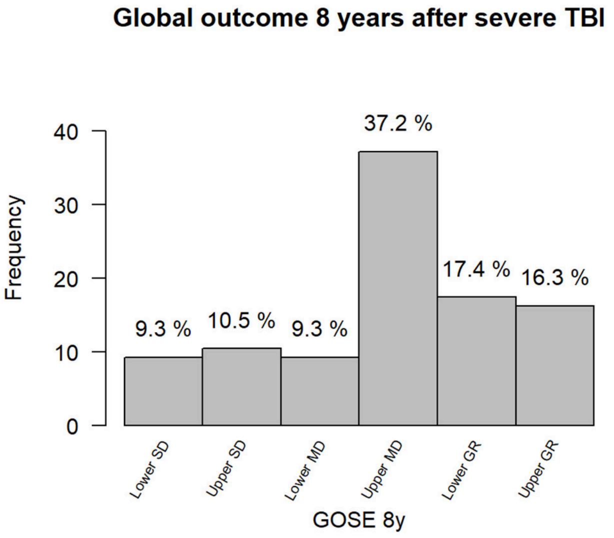

FIGURE 5 | GOSE 8y: Glasgow Outcome Scale Score Extended at 8 years. SD, Severe Disability; MD, Moderate Disability; GR, Good Recovery.

training which was a paid training course for 10 of them (58.8%). Six patients followed a vocational rehabilitation program.

Subjects who had a job were asked for their difficulties at work. The main complaints were fatigue ($n = 19$, 51.4%), irritability and inability to manage emotions ($n = 17$, 45.9%), difficulty in maintaining concentration ($n = 17$, 45.9%), difficulty in dual-tasks ($n = 16$, 43.2%), memory problems ($n = 16$, 43.2%). Rates of difficulties at work are shown in **Figure 7**. The median number of difficulties at work was five (interquartile range, 5). Only two of the 37 subjects declared no difficulties. These difficulties were

TABLE 2 | Years GOSE univariate analysis.

	OR [95% CI] or spearman's rho	*p*-value	Corrected* *p*-value
Age (years) ($n = 86$)	0.977 [0.949–1.004]	0.101	0.909
Gender male ($n = 86$)	0.976 [0.397–2.40]	0.958	1
Education duration (years) ($n = 78$)	1.23 [1.07–1.41]	0.003	0.051
Occupational Class pre-injury ($n = 82$) (ref. blue collar)			
White collar	1.43 [0.537–3.87]	0.472	1
Retired	1.28 [0.163–9.91]	0.81	1
Student	2.92 [1.002–8.69]	0.051	0.56
Unemployed	1.00 [0.235–4.31]	0.998	1
White collar	1.43 [0.537–3.87]	0.472	1
Employed pre-injury ($n = 82$)	0.583 [0.250–1.34]	0.206	1
Living alone pre-injury ($n = 86$)	1.08 [0.467–2.52]	0.854	1
Alcohol abuse ($n = 81$)	0.738 [0.209–2.66]	0.637	1
GCS ($n = 85$)	3.74 [1.40–10.2]	0.009	0.126
Duration of coma (days) ($n = 71$)	0.953 [0.886–1.02]	0.193	1
Time to follow command (days) ($n = 66$)	0.958 [0.915–1.003]	0.068	0.681
Length of stay in ICU (days) ($n = 86$)	0.972 [0.955–0.989]	0.002	0.027
GOS at ICU discharge ($n = 74$)	2.01 [1.20–3.43]	0.009	0.126
GOSE at 1 year ($n = 55$)	5.16 [3.01–9.62]	< 0.001	<0.001
HAD anxiety at 8 years ($n = 76$)	0.884 [0.805–0.969]	0.009	0.126
HAD depression at 8 years ($n = 76$)	−0.498	< 0.001	<0.001
HAD total at 8 years ($n = 76$)	−0.428	< 0.001	0.002
DEX score at 8 years (patients) ($n = 76$)	0.954 [0.924–0.983]	0.003	0.048
DEX score at 8 years (relatives) ($n = 47$)	0.946 [0.910–0.979]	0.003	0.045

TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICU, Intensive Care Unit; GOSE, Glasgow Outcome Scale—Extended; HADS, Hospital Anxiety Depression Scale; DEX, Dysexecutive Questionnaire; OR, Odds Ratio of falling into a upper level of GOSE associated with a one-unit increase of the independent variable.
**Corrected p-value according to Holm.*

considered constant for 6 subjects out of 35 (17.1%), frequent for 11 (31.4%), occasional for 18 (51,5%) and they answered that it disturbed work "a lot" for 8.6%, "a little" for 42.9%, "not at all" for 48.6%. Finally, on the 37 workers, 40.5% answered that their quality of life had improved "enormously," 40.5% "a lot," 16.2% "a little," and 2.7 % "not at all" since they returned to work.

Ten subjects out of the 82 evaluated patients (12.2%), returned to work after the injury and then quit. Three of them (30%), declared a job change and two (20%) a modification of tasks in the same kind of job. Four of these 10 patients had changed employer. These ten subjects returned to work at median 24 months after TBI (interquartile range, 9). They quit at median 21 months (interquartile range, 19.5) later. Job loss was related to TBI according to five of these patients. Three subjects declared they quit work because of difficulties at work, one retired, another stopped work for a professional training, three were at the end of their employment contract and cessation of labor was a personal choice for the last three. Five subjects had professional training since TBI and it was a paid training for two of them. Five had vocational rehabilitation.

Of the 35 patients (42.7% of the 82 evaluated patients) who did not resume work, 31 (88.6%) declared that was because of TBI. Five retired after TBI or were on early retirement. None was a student or in vocational training at the time of evaluation. Six (17.1%) were currently searching for a job. Three (8.6%) were stay-at-home parents. Seven (20%) had an unpaid community-based and voluntary activity.

Univariate analysis of variables associated with return to work 8-year post injury are shown in **Table 4**. After corrections for multiple comparisons, a higher 1-year GOSE score, a lower patient's self-rating DEX score, independence in taking public transports, in finance and administrative management, and resuming of driving were significantly associated with return to work. Subjects who did not resume driving were more likely to be unemployed. There was a non-significant trend after correction for multiple comparison, for pre-injury occupational levels to impact return to work. Adjusted standardized residuals were calculated and showed that only unemployed subjects before TBI were more frequently unemployed 8 years after. There was also a trend for a lower initial GCS score, a longer length of stay in intensive care unit, a lower GOS score upon intensive care unit discharge, a higher HADS depression score, a higher DEX score assessed by a relative, swallowing difficulties, dependence in self-care activities, inability to write a letter to be associated with unemployment.

DISCUSSION

This is one of the first report of long-term outcome over 8 years in a sample of exclusively severe TBI included prospectively from the acute stage and from different emergency centers.

Impairments, Activity Limitations, and Global Outcome

The main results were that very few, only 15% of the evaluated patients did not suffer somatic or neurological disability and most of them reported multiple and various complaints. Balance, motricity, and headaches were the most frequent complaints which corresponds with previous studies of patients recruited from a rehabilitation center (3). The very high rates of cognitive and behavioral problems reported in our sample and the high number of complaints per patient point out that they seemed more disabling than neurological or somatic disorders in the long-term. These results were in line with those reported 10 to 15 years after very severe TBI as defined by a post-traumatic amnesia duration of two months or more (32).

The probability of developing post-traumatic epilepsy increases with TBI severity (33). About 10% of the sample

TABLE 3 | Eight-years GOSE score multivariable analysis.

Variable	Model 1		Model 2	
	Sociodemographic and injury related factors ($n = 60$) OR [95% CI]	p-value	Sociodemographic, injury related and post injury factors ($n = 60$) OR [95% CI]	p-value
Age (years)	0.94 [0.9–0.98]	0.002	0.96 [0.92–1.00]	0.03
Education (years)	1.38 [1.18–1.63]	0.0001	1.3 [1.09–1.56]	0.004
Length of stay ICU	0.97 [0.95–0.998]	0.03	0.98 [0.95–1.01]	0.3
GOS score at ICU discharged	2.19 [1.22–4.02]	0.04	2.11 [1.11–4.08]	0.02
DEX score (patient) at 8 years	–	–	0.96 [0.92–0.99]	0.02

GOSE, Glasgow Outcome Scale—Extended; GOS, Glasgow Outcome Scale; ICU, Intensive Care Unit; DEX, Dysexecutive Questionnaire; OR, Odds Ratio of falling into a upper level of GOSE associated with a one-unit increase of the independent variable.

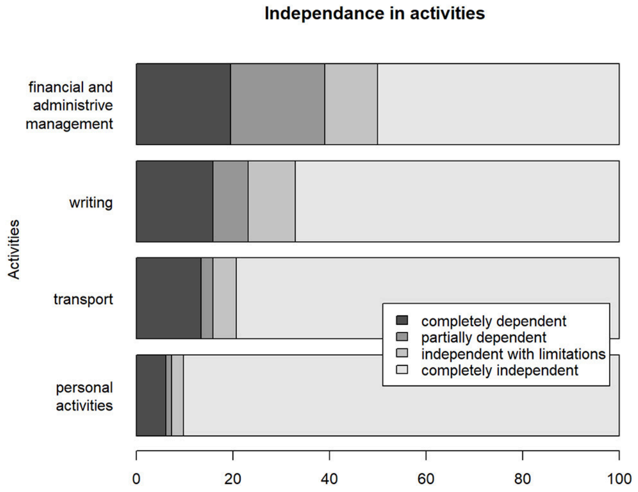

FIGURE 6 | Writing, Write a letter; Transport, Taking public transports; Personal activities, grooming, dressing, moving at home, using the bathroom.

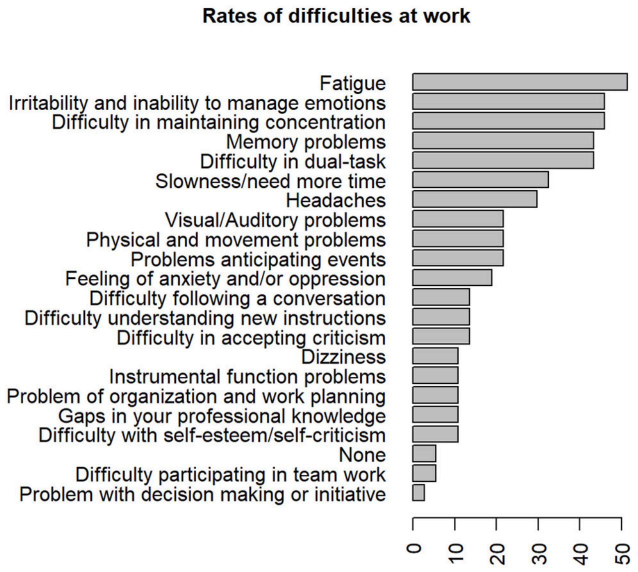

FIGURE 7 | Frequencies of reported difficulties at work 8 years after severe Traumatic Brain Injury.

developed epilepsy and only one patient was not stabilized at 8-year follow-up. This result appeared to be quite similar to those described in previous reports with other TBI severity rating scales (3, 33, 34).

About a quarter of the sample had clinically significant anxiety or depression that seemed consistent with previous reports in long-term follow-up after rehabilitation (35). The management of stress and emotional disorders was among the most frequently perceived needs of patients in previous studies (36, 37).

Global outcome evaluated with GOSE score, revealed that about a third (28%) of the subjects were at a lower moderate disability level or severe disability, meaning they needed help for daily living activities. Another third (37%), were classified at an upper moderate disability level which means they were independent inside and outside the home but had a reduced work capacity, less but some social, and leisure activities or at some weekly family or friendship disruption. The last third (33%) obtained a good recovery according to the GOSE, which was in the upper range for 16%. These results were in line with previous reports with inclusion from acute care and comparable initial severity (38, 39) and worse than those described in studies including also mild and moderate TBI from rehabilitation units (35). In our study as in previous research, age and gender did not significantly influence the GOSE score at 8 years in the univariate analysis (38). However, in the multivariable analysis taking into account injury severity, older age was associated with poorer global long-term outcome as most frequently reported (4). A longer education duration was significantly associated with a better long-term global outcome even when taking into account initial severity in the multivariable model which was an original result not reported so far to our knowledge. Lower initial GCS score, longer length of stay in the intensive care unit, lower GOS score at intensive care unit discharge and lower GOSE score at 1 year were all significantly associated with lower GOSE score at 8 years. To our knowledge, the significant effect of these injury severity markers on long-term global functioning (as measured with GOSE score) in patients with severe TBI had rarely been found in previous research only including patients with severe TBI. Sigurdardottir et al. (40) found that initial TBI severity was significantly related to

TABLE 4 | Return to work. Univariate analysis.

Patient characteristics	Unemployed (*n* = 39)		Employed (*n* = 37)			
	Mean ± SD [minimum; maximum] or count (%)	**Missing data**	**Mean ± SD [minimum; maximum] or count (%)**	**Missing data**	**p (chi^2) p (student)**	**Corrected* p (chi^2) or p (student)**
Gender		0 (0%)		0 (0%)	0.49	1
Femal	6 (15.4%)		9 (24.3%)			
Male	33 (84.6%)		28 (75.7%)			
Age (years)	33.8 ± 11.2 [15.4–52.4]	0 (0 %)	29.9 ± 10.8 [16.3–53.8]	0 (0 %)	0.124	1
Years of education	11.5 ± 3.3 [6–19]	3 (7.7 %)	12.5 ± 2.6 [7–17]	4 (10.8 %)	0.181	1
Occupational class		1 (2.6%)		1 (2.7%)	0.028	0.788
Blue collar	18 (47.4%)		13 (36.1%)			
White collar	7 (18.4%)		13 (36.1%)			
Student	7 (18.4%)		10 (27.8%)			
Unemployed	6 (15.8%)		0 (0%)			
Living alone before TBI		0 (0%)		0 (0%)	0.376	1
No	26 (66.7%)		29 (78.4%)			
Yes	13 (33.3%)		8 (21.6%)			
Alcohol abuse		4 (10.3%)		0 (0%)	0.321	1
No	31 (88.6%)		36 (97.3%)			
Yes	4 (11.4%)		1 (2.7%)			
GCS	5.3 ± 1.8 [3–8]	1 (2.6 %)	6.2 ± 1.7 [3–8]	0 (0 %)	0.039	0.97
Duration of coma (days)	10 ± 6.1 [0–23]	11 (28.2 %)	9.6 ± 6.2 [0–24]	3 (8.1 %)	0.84	1
Time to follow command (days)	13.2 ± 11.5 [0–56]	13 (33.3 %)	13 ± 10.5 [0–50]	5 (13.5 %)	0.946	1
Length of stay in ICU (days)	36.6 ± 28.2 [3–131]	0 (0 %)	24.2 ± 18.6[4–84]	0 (0 %)	0.026	0.766
GOS at ICU discharge	3.5 ± 0.8 [2–5]	8 (20.5 %)	3.9 ± 0.8 [3–5]	2 (5.4 %)	0.036	0.97
GOSE at 1 year	4.2 ± 1.1 [2–7]	15 (38.5 %)	5.5 ± 1.4 [4–8]	13 (35.1 %)	$<$0.001	0.01
HADS anxiety score	6.7 ± 4.7 [0–17]	6 (15.4 %)	5.3 ± 4.4 [0–16]	0 (0 %)	0.193	1
HADS depression score	6.5 ± 4.8 [0–16]	6 (15.4 %)	4.2 ± 4.1 [0–14]	0 (0 %)	0.036	1
HADS total score	13.2 ± 8.1 [1–33]	6 (15.4 %)	9.4 ± 8.1 [0–27]	0 (0 %)	0.059	0.97
DEX score (patients)	21.8 ± 14.1 [3–59]	6 (15.4 %)	11.2 ± 10.7 [0–44]	0 (0 %)	0.001	0.029
DEX score (relatives)	30.2 ± 15.5 [3–71]	11 (28.2 %)	15.9 ± 17.4 [0–62]	23 (62.2 %)	0.015	0.459
Somatic and neurological complaints						
Headaches		5 (12.8%)		7 (18.9%)	0.921	1
No	23 (67.6%)		19 (63.3%)			
Yes	11 (32.4%)		11 (36.7%)			
Other pain		2 (5.1%)		0 (0%)	0.767	1
No	29 (78.4%)		31 (83.8%)			
Yes	8 (21.6%)		6 (16.2%)			
Motricity		2 (5.1%)		0 (0%)	0.097	1
No	18 (48.6%)		26 (70.3%)			
Yes	19 (51.4%)		11 (29.7%)			
Balance		2 (5.1%)		0 (0%)	0.161	1
No	17 (45.9%)		24 (64.9%)			
Yes	20 (54.1%)		13 (35.1%)			
Vision		2 (5.1%)		0 (0%)	0.132	1
No	22 (59.5%)		29 (78.4%)			
Yes	15 (40.5%)		8 (21.6%)			

(Continued)

TABLE 4 | Continued

Patient characteristics	Unemployed ($n = 39$)		Employed ($n = 37$)			
	Mean ± SD [minimum; maximum] or count (%)	**Missing data**	**Mean ± SD [minimum; maximum] or count (%)**	**Missing data**	**p (chi²) p (student)**	**Corrected* p (chi²) or p (student)**
Audition		2 (5.1%)		0 (0%)	0.734	1
No	31 (83.8%)		33 (89.2%)			
Yes	6 (16.2%)		4 (10.8%)			
Swallowing		1 (2.6%)		0 (0%)	0.037	0.97
No	30 (78.9%)		36 (97.3%)			
Yes	8 (21.1%)		1 (2.7%)			
Taste/smell		2 (5.1%)		0 (0%)	1	1
No	28 (75.7%)		27 (73%)			
Yes	9 (24.3%)		10 (27%)			
Lower urinary tract		2 (5.1%)		0 (0%)	0.155	1
No	30 (81.1%)		35 (94.6%)			
Yes	7 (18.9%)		2 (5.4%)			
Spasticity		2 (5.1%)		0 (0%)	0.615	1
No	24 (64.9%)		27 (73%)			
Yes	13 (35.1%)		10 (27%)			
Speech/Language		1 (2.6%)		0 (0%)	0.106	1
No	21 (55.3%)		28 (75.7%)			
Yes	17 (44.7%)		9 (24.3%)			
Independence						
Personal activities		0 (0%)		0 (0%)	0.039	0.97
No	6 (15.4%)		0 (0%)			
Yes	33 (84.6%)		37 (100%)			
Taking public transports		0 (0%)		0 (0%)	0.001	0.026
No	12 (30.8%)		0 (0%)			
Yes	27 (69.2%)		37 (100%)			
Writing a letter		0 (0%)		0 (0%)	0.012	0.366
No	15 (38.5%)		4 (10.8%)			
Yes	24 (61.5%)		33 (89.2%)			
Financial and administrative Management		0 (0%)		0 (0%)	<0.001	0.002
No	25 (64.1%)		6 (16.2%)			
Yes	14 (35.9%)		31 (83.8%)			
Driving		0 (0%)		0 (0%)	<0.001	0.001
No	23 (59%)		4 (10.8%)			
Yes	16 (41%)		33 (89.2%)			

TBI, Traumatic Brain Injury; GCS, Glascow Coma Scale; ICU, Intensive Care Unit; GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale - Extended; HADS, Hospital Anxiety and Depression Scale; DEX, Dysexecutive Questionnaire; Personal activities: grooming, dressing, moving at home, using the bathroom.

**Corrected p-value according to Holm.*

1-year GOSE but they included patients with a much wider range of severity (including mild and moderate TBI)(40). Post-traumatic amnesia has been repeatedly found to be a significant predictor of outcome (3, 40–42). Unfortunately, post-traumatic amnesia was not available in a number of patients in our study and hence could not be included in our model. A higher DEX score rated by patients at 8 years was associated with a poorer global outcome even controlling for age and initial severity. This result confirmed the ecological validity of this scale in measuring cognitive and behavioral difficulties in patients with TBI (23).

Figure 6 shows that most of the patients were independent at home in accordance to GOSE results at 8 years. The independence rate decreased for tasks involving cognitive functions. This was consistent with the fact that cognitive complaints were the most common in these patients. Thus, only half of our sample was independent for financial and administrative management.

Education and Work

All the students at the time of TBI who continued their studies after the trauma had a job at 8 years whereas seven of 11 who did not were unemployed. Academic achievement seemed a good predictor of the ability to work after TBI among students.

In our sample, almost half of the subjects under 65 had a job 8 years after TBI. In contrast, in an earlier study conducted 10 to 15 years after the trauma, 12.5% only had a job, but this was not a longitudinal study, and these patients presumably had a more severe TBI (32). In a more recent study, more than 50% of those studying or employed prior to injury returned to employment (3). In fact, rates reported in literature were very variable as some authors considered return to work and others employment, some included students and others not, TBI severity was not homogenous across studies, patients could be included from acute care or rehabilitation units, and the evaluation period ranged from 1 week to 23 years (42–55). Our results are probably representative of the whole population of patients with severe TBI, as it included patients prospectively followed-up from the day of the accident. However, a recent Nationwide follow-up study using weekly records on public assistance benefits in Denmark reported that only 30% returned to work after severe TBI and 16% achieving stable labor market attachment within 2 years (56).

Among patients with a productive employment, there were important changes in the characteristics of the job. About a quarter decreased their working time which was a slightly higher proportion than previously described (3). However, most of the patients (73%) worked 80% to full time. More than a third of workers reported an income decrease as previously described at 1 year post-TBI (57). On average, return to work occurred more than 2 years after TBI which was in line with previous research (56).

The only demographic or personal characteristic that impacted return to work in our study was the occupational class before TBI. Unemployment before the injury was the only demographic characteristic significantly associated with unemployment after TBI in accordance with previous research (4, 6). We did not find an effect of age on return to work at 8 years. Effect of age was not systematically reported in previous research (4). As in most studies gender was not associated with return to work (4). Length of education was not different between employed and unemployed patients in our sample in contrast with previous studies (6). As patients were more severe in our sample than in most of previous research, a possible explanation was that education duration might have a lower impact on the ability to work in severe TBI subjects than in mild to moderate ones. Regarding TBI severity, there was only a trend for patients with a lower initial GCS score, a shorter length of stay in ICU, a higher GOS score at ICU discharged to be unemployed at 8 years. In previous studies, rate of return to work decreased with TBI severity (6). In our study, because of the important number of evaluated factors, correction for multiple comparisons could have led to a false negative result of the effect of TBI severity on return to work. One year GOSE score was lower in unemployed patients in accordance with our previous findings on the same sample of patients at 4-year assessment (18). Among the variables measured at 8 years, none of the somatic or neurological complaints were associated with return to work. To the contrary, DEX scores assessed with patients was significantly higher in unemployed subjects. These results highlighted that employment on a long-term after TBI was more associated with behavioral than with somatic troubles. There was only a trend, non-significant after correction for multiple comparisons, for higher HADS depression score to be associated with unemployment. Only few previous studies reported a negative association between return to work and depression (58, 59), most of these found no significant association (60). Personality changes have been found significantly associated with unemployment 18 months after severe TBI (61), in accordance with the present results at a longer term post-injury. Finally, not surprisingly, independence in personal care, the ability to use public transport, and to manage administrative duties were all significantly associated with employment.

Limitations

Our study has several limitations. First, a part of the collected data was reported by patients or relatives, and some measures were not obtained for the whole sample because of time required to collect this important amount of data. The second limitation is the high rate of lost to follow-up which is frequent in this kind of long-term follow-up studies (9, 40, 62–64). However, patients lost to follow-up or those who refused to participate only significantly differed regarding pre-TBI occupational status. Hence, our sample seemed representative of the original cohort. However, we could not exclude bias as previous work showed that socially disadvantaged persons were underrepresented in TBI outcome research (22). To avoid this bias and improve the knowledge of TBI outcome and its predictors, future works based on data from national or regional registers as in recent work of Odgaard et al. (56) and confrontation with the initial TBI data would be helpful.

CONCLUSION

We provided a rare comprehensive description of long-term outcome in an inception cohort of exclusively severe TBI patients included at the acute stage. Most important results were the low rate of full recovery on a long-term, the high rates of complaints and particularly those concerning cognitive and behavioral disorders. The long-term global outcome was related to age, education duration, initial injury severity, and persistent dysexecutive syndrome. Return to work remained relatively low and those who had a job still experienced a number of difficulties at work, raising concerns about job stability. Dysexecutive disorders had a significant impact on long-term employment. These results reinforced the importance of long-term follow-up in patients with severe TBI and the need for specific interventions mainly aimed at the management of cognitive disorders and socio-professional reintegration.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

PAz, CJ, EB, PP-D, AR, and JC contributed to the conception and design of the study. GN collected data. IG organized the database and performed the statistical analysis. AR performed the statistical analysis and wrote the first draft of the manuscript. PAz, CJ, EB, AL, and CV-A critically revised the draft and provided updates. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Driving Behaviors 2–3 Years After Traumatic Brain Injury Rehabilitation: A Multicenter Case-Control Study

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Introduction: Driving an automobile is an important activity for the social participation of individuals with traumatic brain injury (TBI). Return to safe driving is usually addressed during rehabilitation, but we know little about driving behaviors in the years following TBI rehabilitation.

Objective: To explore self-reported and objective (official driving records) post-rehabilitation driving behaviors and offenses in individuals with TBI: (a) having passed a driving evaluation, (b) who did not undergo a driving evaluation, and (c) non-injured controls.

Methods: Cross-sectional design with 162 adults: (a) 48 participants with mild, moderate, or severe TBI whose drivers' license was suspended and reinstated following a driving evaluation during rehabilitation (TBI-DE; *M* = 42.2 years of age, *SD* = 11.5); (b) 24 participants with TBI who maintained their driving privileges without undergoing a driving evaluation (TBI-NE; *M* = 36.5 years of age, *SD* = 9.9); (c) 90 non-injured controls (*M* = 43.8 years of age, *SD* = 11.4). Participants with TBI were recruited from seven rehabilitation centers, 2–3 years after the end of rehabilitation in the province of Quebec, Canada. During a telephone interview, data were obtained regarding self-reported driving: (a) habits; (b) self-efficacy; (c) anger expression; (d) sensation-seeking; (e) violations/errors; (f) accidents, driving offenses, and demerit points for the two-year interval predating the study. Objective data for driving offenses, accidents, and demerit points were obtained from the automobile regulatory body for the same period and for the two-year interval before the injury for the TBI groups.

Results: Compared to non-injured controls, the TBI-DE group reported significantly lower scores for self-reported verbal aggressive expression of anger and driving violations/errors. Conversely, their official driving records showed significantly more demerit points for the last 2 years, and a significantly higher frequency of serious post-rehabilitation accidents (10), compared to the TBI-NE group (one) and the control group (none). Compared to pre-injury levels, individuals with TBI had significantly more demerit points post-rehabilitation.

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Conclusions: Individuals with TBI may underestimate risky driving behaviors even if they have been deemed fit to drive. Reduced self-awareness, memory, and dysexecutive problems following TBI could influence self-report of driving behaviors and explain discrepancies between self-reported and objective driving-related behaviors. Recommendations for research and practice are provided.

Keywords: automobile driving, driving behaviors, interdisciplinary neurorehabilitation, road accidents, social participation, traffic offenses, traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a worldwide health problem resulting in long-lasting disability and negative psychosocial consequences, even in individuals with milder injuries (1). Successful return to driving following TBI has been positively associated with return to employment, life satisfaction, maintenance of social relationships, engagement in recreational activities, and community integration and participation (2). As the preferred mode of transport in the western industrialized world (3), driving a vehicle can also be a risky activity for the driver and for the society, with post-crash incapacity varying from 2 to 87% (4). The variability of published post-crash disability rates can be mainly explained by the specific outcome measures used and the modes of data collection and source (e.g., insurance claimants, hospital admissions, community settings). Between 42 and 85.1% of individuals with moderate to severe TBI return to driving and estimations indicate that 63% have not been professionally evaluated for driving competency (5–10). For individuals with severe TBI, a relicensing rate of 50% has been documented following extensive neurorehabilitation (11). Both stricter legal regulations (i.e., society's safety) and the individual with TBI's need to resume driving (i.e., personal safety and autonomy) are reasons for professionals to understand post-TBI driving behaviors and to develop reliable tools for their assessment (12).

Regarding the time necessary to return to driving, the results of a multicenter study indicated that 42% of individuals with TBI had returned to driving 1 year post-injury and the percentage increased to 53% at 5 years post-TBI (13). Even when individuals with milder injuries returned to driving faster, after 5 years, the severity of TBI was not a factor. Compared to pre-injury levels, estimates indicate that individuals with TBI changed their driving behaviors post-injury, including driving less frequently (e.g., 92.5% of drivers reported driving nearly every day pre-injury compared to 78.3% post-injury), driving more slowly (40.6%), limiting their driving times (36.8%), experiencing greater difficulties planning and remembering routes (41.5%), driving with fewer passengers (16%), avoiding night driving (24.5%), avoiding busy traffic (37.7%), and unfamiliar areas (19.8%), and more near-crashes (20%) (14, 15).

Driving can be an automatic and over-learned activity for experienced drivers, but it is far from being a routine activity because cognitive functions are necessary to effectively respond to changing environments and the continuing flood of complex information (12, 16). Cognitive deficits associated with TBI (17) may prevent individuals with TBI from driving safely, and compromise the driver's safety and that of other road users (18). Slowed reaction times (19), attentional problems (20, 21), anosognosia (22, 23), visuospatial problems (24–26), and dysexecutive symptoms (including behavioral and emotional control) (27, 28) have been associated with reduced fitness to drive (29). Neuropsychological assessment and on-road driving evaluations have been widely used to estimate the ability to resume driving following TBI (30, 31).

However, there are relatively few studies investigating driving behaviors in individuals who have returned to driving following a TBI with discordant findings. For example, the results of a study aiming to determine the frequency of road traffic accidents in 60 adults following severe TBI indicated that although 50% resumed driving, 63% of them were involved in traffic accidents with personal responsibility in 26/36 accidents (32). The authors concluded that compared to pre-injury levels, individuals with severe TBI who resume driving presented twice the risk of causing a road traffic accident. Also, in a study with a sample of 90 family caregivers of individuals with severe TBI, 32% of their care recipients had resumed driving but 38% of them had been involved in road traffic accidents (33). Compared to normative data, another study reported that the accident rate in individuals with TBI was more than two times higher (34). Furthermore, it was shown that individuals with acute mild TBI as well as individuals with TBIs of varying severities were slower than matched controls with minor orthopedic injuries or than non-injured controls, respectively, in responding to traffic hazards as presented in an experimental video task (35, 36).

In contrast, a recent meta-analysis including eight studies published between 1990 and 2015 indicated that there were no significant differences between individuals with TBI and non-injured individuals in the objective risk of motor vehicle collisions (37). This meta-analysis also demonstrated that based on self-reported data, the risk for motor vehicle collisions was surprisingly higher for non-injured individuals. But still, data showed that individuals with TBI performed worse during on-road assessments and had more problems with vehicular control. A previous review comprising selected studies which included at least 100 participants, control groups, and investigated chronic effects (6 months or longer) concluded that TBI did not lead to increased risks for crashes or driving violations (38). However, this review called attention on other issues that may affect driving, such as the propensity for risk-taking behavior (39), anger issues that may result in later driving problems (40), and the role of executive functions in driving (41). The authors suggested the need to include return to driving as an outcome and the importance of studying the effects of risk-taking and anger issues on driving behaviors after TBI. The aforementioned inconsistencies in outcomes may in part be due to varying levels of availability and access to neurorehabilitation and driving evaluation services across study settings. Also, inconsistencies could be explained by methodological differences between studies for data sources (e.g., self-reported vs. official records) and variables such as driving exposure/experience and TBI severity that are not systematically reported.

The current study thus aimed to explore self-reported and objective (data from official driving records) driving behaviors and offenses in a group of: (a) individuals with TBI, 2–3 years after the end of rehabilitation, who had been evaluated for driving ability following their TBI and deemed fit to return to driving (TBI-DE); (b) individuals with TBI, 2–3 years post-rehabilitation, who had continued to drive following their TBI and did not require a driving evaluation (TBI-NE); and (c) non-injured drivers from the general population. The main objectives were to: (a) compare self-reported driving behaviors and road offenses (i.e., driving habits, driving self-efficacy, driving anger expression, driving-related sensation-seeking, and driving violations/errors, as well as the number of road accidents, driving offenses, and demerit points) between the three groups of participants; (b) compare data from official driving records (i.e., number of road accidents, their seriousness, driving offenses, and demerit points) between the three groups of participants; (c) compare pre-injury and post-rehabilitation data from official driving records (i.e., number of accidents, their seriousness, driving offenses, and demerit points between the two TBI groups; and (d) explore the relationship between self-reported driving behaviors, and number of accidents and offenses in driving records of participants with TBI post-rehabilitation.

This study was conducted within a publicly funded and universally accessible TBI continuum of care. When needed, comprehensive person-centered interdisciplinary neurorehabilitation is freely available to individuals with TBI. Furthermore, the driving license of an individual with TBI is systematically suspended when indicated by the medical and rehabilitation staff. Within the continuum of care, individuals with TBI are referred to one of the driving evaluation programs in the rehabilitation centers for an evidence-based formal assessment of driving fitness. As such, this is a rehabilitation context with equality of access and systematic referral for evaluation of driving fitness. Given the context of unequal access to rehabilitation in which most of the previous studies have been conducted, the discordant results could be in part due to differential access to neurorehabilitation and driving evaluation services. Based on this context permeating our hypotheses, we anticipated that the TBI-DE group would mainly comprise individuals with moderate to severe TBI. Considering the previously highlighted long-term post-TBI cognitive and behavioral issues affecting driving that often persist even following neurorehabilitation, we hypothesized that the TBI-DE group, but not the TBI-NE group, would present more objective road accidents and offenses in the last 2 years (i.e., post-rehabilitation) compared to non-injured controls, but that their self-reported driving behaviors (i.e., driving self-efficacy, anger expression, sensation-seeking, violations/errors) would be similar to those of the other two groups. Given the discordant findings in the literature, we did not anticipate any hypotheses for objectives c and d given their exploratory nature.

METHODS

Participants

A total of 162 participants took part in this study, including a convenience sample of 72 adults with TBI, and 90 non-injured controls. Participants with TBI were recruited from TBI rehabilitation programs in seven different neurorehabilitation centers across Quebec, Canada. The TBI-DE group consisted of 48 adults whose license had been suspended after the injury (based on a medical decision while in hospital or during rehabilitation) and reinstated following a driving evaluation during outpatient rehabilitation. The TBI-NE group included 24 adults with TBI who had maintained their driving privileges without undergoing a driving evaluation. Non-injured controls included 90 adults without any diagnosed neurological or psychiatric disorder.

Participants with TBI were recruited based on the following inclusion criteria: (a) adults having received a diagnosis of TBI, according to the TBI guidelines put forward by the Quebec Ministry of Health (42), with a mild (Glasgow Coma Scale—GCS score 13–15), moderate (GCS score 9–12) or severe TBI (GCS score 3–8); (b) 18 to 60 years of age; (c) having participated in an interdisciplinary comprehensive rehabilitation program following their TBI; (d) between 2 and 3 years post-TBI rehabilitation; and (e) possession of a valid driver's license. Non-injured controls were recruited based on the following inclusion criteria: (a) 18–60 years of age; (b) self-report of an absence of any diagnosed neurological or psychiatric disorder; and (c) possession of a valid driver's license. All participants reported driving an automobile more than 1,000 km/year in the previous 2 years, as well as in the 2 years predating the injury for the TBI groups. The demographic characteristics and injury-related variables for the three groups are reported in **Table 1**.

Procedure

The Research Ethics Board (REB) of the Center for Interdisciplinary Research in Rehabilitation of Greater Montreal of the *CIUSSS du Centre-Sud-de-l'Île-de-Montréal (CIUSSS CSMTL)* approved the current study. Recruitment took place between September 2013 and March 2016. Participants with TBI were recruited from seven rehabilitation centers in the province of Quebec providing driving evaluation programs for individuals with motor, perceptual, or cognitive disabilities. These programs offer fitness to drive assessments, driving skills training, and vehicle adaptation services to individuals referred from other programs within the rehabilitation centers or from outside sources. Research coordinators from the rehabilitation centers contacted potential participants with TBI (TBI-DE and TBI-NE groups) who had finished their rehabilitation program between September 2010 and March 2013 (i.e., 2–3 years post-rehabilitation) and invited them to participate in the

TABLE 1 | Demographic, injury-related characteristics, and driving habits for the TBI-DE, TBI-NE, and non-injured control groups.

Variables	**TBI-DE *(n = 48)***		**TBI-NE (*n* = 24)**		**Non-injured controls (*n* = 90)**	
	***N* (%)**	***M* (*SD*)**	***N* (%)**	***M* (*SD*)**	***N* (%)**	***M* (*SD*)**
Sex						
Male	35 (73)		12 (50)		54 (40)	
Female	13 (27)		12 (50)		36 (40)	
Age (years)*		42.2 (11.5)		36.5 (9.9)		43.8 (11.4)
Injury severity***						
Mild TBI	13 (27.1)		18 (75)		–	–
Moderate TBI	11 (22.9)		4 (16.7)		–	–
Severe TBI	24 (50)		2 (8.3)		–	–
Driving experience (months)**		300 (135)		199 (94)		301 (123)
Kilometers traveled per year		19 082 (24 827)		14 388 (10 319)		16 319 (18 825)
Preferred route taken						
Less than 10 km	9 (6)		7 (4)		20 (12)	
Between 10 and 50 km	23 (14)		9 (6)		47 (29)	
Between 51 and 100 km	4 (3)		1 (1)		7 (4)	
More than 100 km	1 (1)		4 (3)		2 (2)	
Variable distances	11 (7)		3 (2)		14 (9)	
Access to *SAAQ* Records***						
Yes	30 (62.5)		19 (79.2)		22 (24.4)	
No	18 (37.5)		5 (20.8)		68 (75.6)	

SAAQ, Automobile Insurance Board of Quebec (Société d'Assurance Automobile du Québec). **$p < 0.05$*, ***$p < 0.01$*, ****$p < 0.001$.*

study. Non-injured controls from the community were recruited by the professional external interview agency that conducted the interviews. A financial compensation of 15$CAD was provided to all participants.

Data were gathered using a semi-structured telephone interview conceived by the research team, records from the Automobile Insurance Board of Quebec (*Société d'Assurance Automobile du Québec-SAAQ*), and medical records. Participants provided informed consent to participate in the study and could also accept or deny access to their driving records. Access to medical records of participants with TBI also required informed consent. Telephone interviews were conducted by a professional external interview agency (e.g., 30 min approximately, using verbatims provided by the research team). During the telephone interview, non-injured controls and participants with TBI provided information (i.e., self-report) for the previous 2 years (i.e., post-rehabilitation for the TBI groups) regarding their driving habits (i.e., driving experience in months, number of kilometers traveled per year, and most frequent type of route taken in terms of traveling distances), as well as the number of road accidents, number of driving offenses, and demerit points. Objective data for road accidents, the seriousness of accidents (i.e., minor collisions vs. accidents resulting in bodily harm or death, as defined by the *SAAQ* regulatory body), driving offenses and demerit points were also obtained from participants' official driving records for the previous 2 years for all participants (i.e., 2–3 years post-rehabilitation for the TBI groups), as well as for the 2 years preceding injury in the TBI groups. In the province of Quebec, demerit point brackets are determined on the basis of the type of license, where a four-point bracket applies to holders of a learner's license or those who have held their license for fewer than 5 years, and 8-, 12-, and 15-point bracket apply, respectively to driver's license holders under age 23, aged 23 or 24, or aged 25 or older (*SAAQ*, https://saaq.gouv.qc.ca/en/drivers-licences/demerit-points/). During the telephone interview, self-reported driving behaviors were measured for all participants using the following outcome measures.

Measures

Driving Self-Efficacy Scale (DSES)

The DSES is a self-report 12-item questionnaire to estimate the perception of driving abilities (43). Using a 7-point Likert scale (ranging from 1 = "Certainly so" to 7 = "Certainly not"), respondents indicate their agreement (e.g., "Driving a car is easy"). Three items are reverse-scored (i.e., 10, 11, and 12). Means of self-ratings across items are calculated; higher scores indicate better driving self-efficacy. The DSES has shown good internal consistency for the original English version (Cronbach's $\alpha = 0.92$) (43) and the French version (Cronbach's $\alpha = 0.88$) (44). Bourrat et al. (45) adapted the French version to individuals with brain injury (Cronbach's $\alpha = 0.87$).

Driving Anger Expression Inventory (DAX)

The DAX is a 49-item questionnaire used to estimate the expression of anger on the road including constructive coping and expression of anger while driving (46). Respondents are asked to rate the frequency of specific reactions while driving in a four-point scale (i.e., 1 = "Almost never" to 4 = "Almost always"). The DAX captures four different dimensions: (a) verbal aggressive expression (12 items; e.g., "Swear at the driver aloud"), (b) use of the vehicle to express anger (11 items; e.g., "Do to drivers what they did to me"), (c) personal physical aggressive expression of anger (11 items; e.g., "Try to get out and have a physical fight"), and (d) adaptive/constructive expression of anger (15 items; e.g., "Accept there are frustrating situations"). The DAX has shown evidence of validity and reliability with internal consistency for its subscales (Cronbach's α ranging from 0.84 to 0.89) (47). Mean of self-ratings across items are calculated for each subscale; higher scores indicate increased levels of anger expression (i.e., subscales a, b, and c) or the use of a more adaptive expression of anger (i.e., subscale d). For this study, we used the French version of the DAX that includes three dimensions: (a) verbal aggressive expression, (b) use of the vehicle to express anger, and (c) adaptive/constructive expression of anger (48, 49). Factor analysis of the French version of the DAX supports the removal of the dimension about the personal physical aggressive expression of anger, with acceptable to satisfactory internal consistencies for the remaining dimensions (Cronbach's α between 0.64 and 0.83) (48, 49).

Driving-Related Sensation-Seeking Questionnaire (DRSS)

The DRSS is a 7-item self-report questionnaire that assesses physical and social risk-taking while driving (50). The DRSS has been adapted to French (51). Internal consistencies have been established for both the English (Cronbach's $\alpha = 0.84$) (50) and the French version (Cronbach's $\alpha = 0.68$) (51). Respondents are asked to rate each item on a 5-point scale ranging from 1 (i.e., "not true at all") to 5 (i.e., "absolutely true") (e.g., "I often feel like being a racing driver"; "I would like to learn how to drive cars that can go faster than 300 km/h"). Mean scores of self-ratings across items are calculated and higher mean scores indicate more driving-related sensation-seeking.

Driving Behavior Questionnaire (DBQ)

The driving behavior questionnaire is a self-report 12-item questionnaire to evaluate behaviors related to driving violations and errors (52, 53). Respondents rate the frequency of each behavior using a 6-point Likert scale ranging from 0 (i.e., "Never") to 5 (i.e., "Nearly all the time"). The DBQ captures three different dimensions: (a) fast driving (5-items; e.g., "Speeding on a residential road"), (b) maintaining progress (4-items; e.g., "Jumping lights"), and (c) anger/hostility (3-items; e.g., "Sounding horn"). Mean scores of self-ratings across items are calculated and higher scores suggest more driving violations and errors while driving. It has been adapted to French (11-item, 4-point Likert scale) from its original format with very good reliability (Cronbach's $\alpha = 0.86$) (48).

Statistical Analyses

Statistical analyses were conducted with IBM SPSS® version 25 (54). Descriptive statistics (means, standard deviations, percentages) were calculated for the variables of interest. One-way between-groups analyses of variance and Tukey HSD *post-hoc* tests or independent-samples *t*-tests were conducted to compare participants' characteristics, driving habits (e.g., age, driving experience in months, and kilometers traveled per year), and driving behaviors (e.g., self-reported driving self-efficacy, driving anger expression, driving-related sensation-seeking, driving violations/errors, as well as self-reported, and official records of number of road accidents, driving offenses, and demerit points). Chi-square or Fisher's exact tests were computed to evaluate differences in sex, TBI severity, type of route taken, and seriousness of accidents (i.e., minor collisions or accidents resulting in bodily harm or death) between the three groups. Paired-samples *t*-tests were calculated to compare pre-injury and post-rehabilitation official records of number of accidents, driving offenses, and demerit points in participants with TBI. Pearson product-moment correlation coefficients were calculated to examine, for the past 2 years in participants with TBI (i.e., post-rehabilitation), the relationships between self-reported driving behaviors, and objective number of accidents and driving offenses. Correlation coefficients were interpreted using the following guidelines for the behavioral sciences (55): (a) small ($r = 0.1$–0.29), (b) medium ($r = 0.3$–0.49), and (c) large ($r = 0.5$–1). Statistical significance was set at an alpha level of 0.05.

RESULTS

Participants' Characteristics and Driving Habits

As indicated in **Table 1**, there were no statistically significant differences regarding sex between the three groups. There was a statistically significant difference in age, $F_{(2,\,159)} = 4.01$, $p = 0.02$. The effect size (eta squared) was small, at 0.04. *Post-hoc* comparisons indicated that the TBI-NE group was younger than the control group. There were no statistically significant differences in age between the TBI groups or between the TBI-DE group and the control group. Regarding injury severity, the TBI-DE group had more participants with moderate and severe injuries (72.9%) than the TBI-NE group, which comprised mainly individuals with mild injuries (75%), X^2 (2, $n = 72$) = 16.52, $p = 0.0003$.

In terms of driving habits, there was a statistically significant difference in months of driving experience between the three groups, $F_{(2,\,159)} = 6.98$, $p = 0.001$. The effect size (eta squared) was medium, at 0.08. *Post-hoc* comparisons indicated that the TBI-NE group had significantly fewer months of driving experience as compared to the TBI-DE group and the control group. There were no significant differences between the TBI-DE and the control group in months of driving experience. There were no significant group differences in kilometers traveled per year. Preferred traveling distances in terms of routes taken were also similar in the three groups, with distances between 10 and 50 km being the most frequently driven. Compared to participants with TBI, the non-injured control group was less likely to authorize access to their driving records, X^2 (2, $n = 162$) = 32.71, $p = 0.00001$.

Self-Reported Driving Behaviors

As shown in **Table 2**, the mean scores for the groups with TBI (TBI-DE and TBI-NE) and the non-injured controls did not differ significantly in terms of self-reported behaviors related to driving self-efficacy (DSES), driving-related sensation-seeking (DRSS), or the use of a vehicle to express anger (DAX subscale). On the contrary, there was a statistically significant main effect, with a small effect size just below the medium range, for verbal aggressive expression of anger (DAX subscale). *Post-hoc* comparisons indicated significantly lower mean scores for verbal aggressive expression of anger in the TBI-DE group compared to the control group. Mean scores for the verbal aggressive expression of anger were comparable between the TBI-DE and the TBI-NE groups, and between the TBI-NE and the control group. In addition, there was a statistically significant main effect, with a small effect size, for driving violations/errors (DBQ). *Post-hoc* tests showed that the TBI-DE group reported significantly fewer driving violations/errors than the TBI-NE group, but there were no statistically significant differences between each of the TBI groups and non-injured controls.

Self-Reported and Objective Road Accidents, Offenses, and Demerit Points

As shown in **Table 3**, the three groups did not differ in terms of self-reported number of accidents, driving offenses or the number of demerit points for the past 2 years (i.e., post-rehabilitation for TBI groups). However, based on objective driving records, there was a significant main effect, with a medium-almost large effect size, for the number of demerit points in the last 2 years. *Post-hoc* analyses indicated that the TBI-DE group had significantly more demerit points compared to non-injured controls. The TBI-DE group also showed a tendency, with a medium effect size, toward more driving offenses in the past 2 years, but this difference did not reach statistical significance. There were no significant differences between the TBI groups in pre-injury number of accidents, driving offenses or demerit points documented in driving records.

Fisher exact tests showed a strong significant between-group effect for the seriousness of accidents documented in driving records post-rehabilitation ($p = 0.0003$, two-tailed). The TBI-DE group had a significantly higher frequency of serious accidents resulting in bodily harm or death in the last 2 years (10 serious accidents with two minor accidents), compared to the TBI-NE group (one serious accident with four minor accidents) and the non-injured control group (no serious accidents with four minor accidents). As for differences in pre-injury seriousness of accidents between the TBI groups as documented in driving records, there was a tendency for a higher frequency of serious accidents in the TBI-DE group (four serious accidents without minor accidents) compared to the TBI-NE group (no serious accidents with two minor accidents) ($p = 0.06$, two-tailed).

Comparison between pre-injury and post-rehabilitation objective data from driving records revealed that for both the TBI-DE, $t_{58} = 2.59$, $p = 0.01$, and TBI-NE groups, $t_{36} = 2.08$, $p = 0.04$, the number of demerit points was significantly higher post-rehabilitation than before the injury with a medium-almost large effect size, (both Cohen's d values 0.67). There were no statistically significant differences between the pre-injury and post-rehabilitation number of accidents or driving offenses for the TBI-DE and TBI-NE groups.

Relationships Between Post-rehabilitation Self-Reported Driving Behaviors, and Objective Accidents and Offenses in Participants With TBI

Pearson product-moment correlation coefficients were calculated between post-TBI rehabilitation (i.e. last 2 years) objective accidents and offenses, and self-reported driving behaviors. In the TBI-DE group, there was a medium, negative association between the level of verbal aggressive expression of anger (DAX subscale) and the objective number of accidents ($r = -0.39$; $p < 0.05$). Conversely, the TBI-NE group showed strong positive relationships between the level of verbal aggressive expression of anger and the number of accidents ($r = 0.54$; $p < 0.05$), as well as driving offenses ($r = 0.47$; $p < 0.05$). The TBI-NE group also showed a medium, positive relationship between the level of driving-related sensation-seeking (DRSS) and the number of driving offenses ($r = 0.46$; $p < 0.05$), as well as a strong negative association between the level of adaptive/constructive expression of anger (DAX subscale) and the number of accidents ($r = -0.6$; $p < 0.01$). There were no statistically significant associations in the TBI-DE group. There were no significant correlations for self-reported driving behaviors with age, injury severity, or driving experience.

DISCUSSION

The current study explored self-reported and objective driving behaviors and offenses in individuals with TBI, 2–3 years post-rehabilitation, having (TBI-DE) or not having undergone a driving evaluation (TBI-NE), with non-injured drivers from the general population. To our knowledge, this is the first multicenter study comparing self-reported and objective driving behaviors in individuals with TBI with or without a driving evaluation, 2–3 years post-rehabilitation, with a non-injured control group. Results show that compared to the TBI-NE and control groups, the TBI-DE group (which comprised mostly individuals with moderate or severe TBI) showed lower or similar self-reported anger- and error-related driving behaviors 2–3 years post-TBI rehabilitation. In contrast, their official driving records (but not their self-report) indicated the presence of a higher number of demerit points and serious accidents. These findings, which have potentially significant public health implications, are generally in line with our hypotheses, although it was not anticipated that the TBI-DE group would report significantly less driving anger expression or errors in driving behaviors. As expected, the TBI-DE group was comparable to the other groups in terms of self-reported driving self-efficacy,

TABLE 2 | Means, standard deviations, and analyses of variance for self-reported driving behaviors in the TBI-DE, TBI-NE, and non-injured control groups.

Self-reported driving behaviors*	TBI-DE ($n = 48$)		TBI-NE ($n = 24$)		Non-injured controls ($n = 90$)		$F_{(2, 159)}$	p	η^2
	M	***SD***	***M***	***SD***	***M***	***SD***			
Driving self-efficacy (DSES)	3.78	0.29	3.82	0.29	3.86	0.31	1.25	0.29	0.02
Driving anger expression inventory (DAX)									
Verbal aggressive expression of anger	1.40	0.39	1.52	0.36	1.60	0.41	4.06	0.02	0.05
Use of the vehicle to express anger	1.11	0.15	1.12	0.14	1.15	0.16	1.25	0.29	0.02
Adaptive/constructive expression of anger	2.89	0.69	2.86	0.53	2.85	0.61	0.05	0.95	0.00
Driving-Related Sensation-seeking (DRSS)	1.86	0.46	2.14	0.85	2.04	0.55	2.28	0.10	0.03
Driving behavior questionnaire (DBQ)	1.26	0.24	1.43	0.42	1.33	0.24	3.14	0.04	0.04

**Self-reported driving behaviors at the time of the study (i.e., 2–3 years post-rehabilitation for TBI groups).*

TABLE 3 | Means, standard deviations, *t*-tests, and analyses of variance for self-reported and objective road accidents, offenses, and demerit points in the TBI-DE, TBI-NE, and non-injured control groups.

Driving accidents, offenses and demerit points	TBI-DE ($n = 48$)		TBI-NE ($n = 24$)		Non-injured controls ($n = 90$)		$F_{(2, 159)}$	p	η^2
	M	***SD***	***M***	***SD***	***M***	***SD***			
SELF-REPORT PAST 2 YEARS*									
Number of accidents	0.31	0.47	0.21	0.41	0.23	0.43	0.66	0.52	0.008
Number of driving offenses	1.71	0.91	1.56	1.33	1.40	0.71	0.55	0.58	0.02
Demerit points	1.32	2.30	1.22	2.41	0.88	1.87	0.77	0.46	0.009
	TBI-DE ($N = 30$)		**TBI-NE ($N = 19$)**		**Non-injured controls ($N = 22$)**		$F_{(2, 68)}$ **or** $t_{(47)}$	p	η^2 **or Cohen's** d
	M	***SD***	***M***	***SD***	***M***	***SD***			
OFFICIAL DRIVING RECORD									
Number of accidents past 2 years*	0.37	0.56	0.26	0.65	0.18	0.40	0.75	0.47	0.02
Number of accidents pre-injury**	0.20	0.48	0.16	0.50	–	–	0.28	0.78	0.08
Number of driving offenses past 2 years*	1.13	1.48	0.79	0.92	0.41	0.80	2.47	0.09	0.06
Number of driving offenses pre-injury**	0.67	1.12	0.47	0.84	–	–	0.67	0.51	0.20
Demerit points past 2 years*	3.17	4.26	2.63	2.63	0.82	1.59	3.54	0.03	0.10
Demerit points pre-injury**	0.93	2.05	1.00	2.19	–	–	0.11	0.91	0.03

**Self-reported and objective accidents and offenses in the 2 years preceding the study, i.e., 2–3 years post-rehabilitation for TBI groups.*
***Objective driving accidents and offenses in the 2 years preceding injury for TBI groups.*

driving-related sensation-seeking, and the use of the vehicle to express anger. Of note, there were no group differences in the number of kilometers driven per year and usual traveling distances, indicating that driving habits were similar in the three groups.

Our results suggest that individuals with TBI, in particular those with moderate to severe TBI that have undergone a driving evaluation to get their drivers' licenses reinstated after the injury (i.e., TBI-DE group), may overestimate their driving abilities even though they present more serious accidents and demerit points as documented in driving records. This is further supported by the negative association between self-reported verbal aggressive anger expression and the number of documented accidents post-rehabilitation in this group. That is, participants in the TBI-DE group who reported lower levels of verbal aggressive expression of anger appear to be those who presented more serious accidents. These findings are compatible with a study comparing self-report and motor vehicle records in 47 individuals with TBI who successfully completed a comprehensive driving evaluation and 22 healthy controls (10). All participants self-rated themselves as having excellent or nearly excellent driving skills, indicating that the TBI group had strong confidence in their driving skills at 2.1 years following a driving evaluation. The results of the current study are also in line with another report addressing the cognitive and personality determinants of post-injury driving fitness in 178 individuals with TBI and stroke, where a measure of sensation-seeking turned out to be unrelated to fitness to drive (56). In their study, cognitive ability measures were more important in predicting fitness to drive than driving-related personality traits in individuals with TBI and stroke. Thus, it is not surprising that in the present study driving-related sensation-seeking was not different in participants with TBI and healthy controls.

The presence of more serious road accidents 2–3 years post-rehabilitation in the TBI-DE group is compatible with the results of a study conducted in individuals with severe TBI who resumed driving and presented twice the risk of causing road traffic accidents as compared to pre-injury levels (32). To our knowledge, only the Schultheis et al. (10) study previously examined driving behaviors using a similar methodology (telephone questionnaires and motor vehicle records) including both individuals with TBI having completed a comprehensive, multilevel driver evaluation program, and healthy controls in the United States. Although the authors did not investigate individuals with TBI having received rehabilitation including or not a driving evaluation, our findings are in the same direction of their study. They found that even if the difference was not statistically significant, individuals with TBI were 1.5 times more likely to report being involved in one or more unreported accidents (i.e., minor accidents that did not involve police or insurance documentation) than healthy controls. On the contrary, participants in the control group ($n = 12$, 54.5%) reported taking part in significantly more unsafe driving situations than the group of individuals with TBI ($n = 8$, 20%). This difference can possibly be explained by the fact that their sample of individuals with TBI reported driving less than the sample of healthy controls, and since they measured only minor accidents. Another study showed that drivers having been assessed for driving fitness generally reported modifying their driving behaviors and did not report more crashes compared to pre-injury (15). However, the authors did not compare self-reported data to official driving records. In our study, with similar driving habits (i.e., kilometers driven per year and traveling distances) across groups and separating those who underwent a driving evaluation from those who did not (i.e., TBI-DE and TBI-NE groups, respectively), participants with TBI had a similar post-rehabilitation number of objective minor collisions as controls, but the group having undergone a driving evaluation (comprising 73% of participants with severe and moderate TBI) had more accidents causing death or bodily harm.

Correlational patterns between self-reported driving behaviors and the number of accidents post-rehabilitation were different for the two groups of participants with TBI. Contrary to the TBI-DE group, the group of participants with TBI who did not require a driving evaluation showed positive associations between the aggressive expression of anger or sensation-seeking and the number of accidents and/or driving offenses. Furthermore, this group showed a negative association between self-reported adaptive/constructive expression of anger and the number of accidents post-rehabilitation. Such associations were not present in the group of participants with TBI having passed a driving evaluation. Research conducted with non-injured individuals has suggested similar trends. For example, a study conducted in drivers who did and did not acknowledge problems with driving anger demonstrated that compared to low anger drivers in both groups, high anger drivers engaged in more aggressive and risky behavior on the road and experienced more accident-related outcomes (57). However, it should be underscored that comparisons between pre-injury and post-rehabilitation data from driving records indicated that both TBI groups showed a significantly higher number of demerit points 2–3 years post-rehabilitation. This could suggest that compared to pre-injury levels, the TBI-NE group also shows a high risk for driving offenses leading to demerit points post-rehabilitation. This finding has significant clinical impacts with respect to insuring, during rehabilitation, optimal screening procedures for potentially risky drivers following TBIs of all severities.

Interestingly, even though the number of pre-injury self-reported and objective accidents, offenses and demerit points was similar in the two groups of participants with TBI, the TBI-DE group showed a pre-injury tendency toward more serious accidents. This may be an indication that some individuals in this group were already more at risk for road accidents before their TBI. Hence, even before the injury they could have evaluated themselves as better drivers than they really were, and in turn have a higher predisposition to suffer a (possibly more severe) TBI during a motor vehicle accident. Although this was not an objective of the present study, future research should specifically study the relationships between mechanism of injury and TBI severity, and pre-post TBI driving behaviors as well as road accident/offense history. The literature does suggest that certain groups are more vulnerable to the risk associated with driving. For instance, under different driving conditions, there is a dramatic increase in driving risk among adolescents in the transition period to independent driving (58). Males (59), college students (60), veterans and older adults (61), and individuals with low socioeconomic status or being part of racial/ethnic minorities (62) are at risk for poorer road safety outcomes. Future studies with larger sample sizes could investigate such associations to provide more insight into the relationships between pre-injury and post-rehabilitation driving risks and behaviors in individuals with TBI.

In sum, individuals with TBI, even though they have passed a driving evaluation, may represent a subgroup that is at risk in driving situations since they rated their driving behaviors as being similar to, or better than, non-injured controls even though they presented more serious accidents and demerit points in their driving records than healthy controls in the community. Furthermore, individuals with TBI who have not been identified as needing a driving evaluation during rehabilitation (e.g., individuals with mild or moderate TBI) may also be at risk for increased road offenses resulting in demerit points in the years following rehabilitation. These original findings bring driving safety following a TBI to the forefront in terms of public health and warrant more systematic processes for insuring safe driving following TBI rehabilitation. Problems with self-awareness and executive functions, often seen in more moderate to severe TBIs (but also present in milder TBIs), could be at the basis of these findings, as may be post-TBI memory problems in general (29, 32, 41, 63). Memory problems could also explain between-group differences for self-reported data when compared to official driving records for the number of accidents, driving offenses, and demerit points.

Limitations and Future Directions

Limitations of this study include self-selection and self-reporting bias, the characteristics of the sample, and the research design. Self-selection bias is inherent to these types of studies. Participants who volunteer for studies on driving may generally find themselves safer to drive (although they may not be aware of their risky driving behaviors). In some cases, individuals may decline participation out of fear that their driving license will be suspended or because they are uncomfortable with the study objectives (3). That could explain, in part, the major trend for non-injured participants to refuse access to their driving records. In the present study, while self-reported driving behaviors were obtained from all participants in the three groups (TBI-DE, TBI-NE, non-injured controls), and the majority of individuals in both TBI groups gave access to their driving records for comparison purposes, a significant proportion of controls did not give such access. This thus warrants caution when interpreting TBI vs. control group differences in objective driving data. Regarding the characteristics of the sample, the TBI-NE group included participants who were younger than the control group, had milder injuries than the TBI-DE group, as expected (this latter difference being inherent to our study objectives comparing groups of individuals with TBI having been referred or not for a driving evaluation), and had less driving experience than the two other groups. However, age, severity, and driving experience did not show a relationship with self-reported driving behaviors neither in the TBI-NE group nor in the TBI-DE group, indicating that they did not appear to influence the results in our study.

For administrative reasons, we were not able to document some characteristics including the cause of the TBI, the exact time between the end of rehabilitation and the completion of the telephone interview (although the interval was limited between 2 and 3 years after the end of rehabilitation for all individuals with TBI), and the date of the driving evaluation (although the driving evaluation is usually conducted within a 1-year interval before the end of rehabilitation). In addition, we did not measure cognitive and psychological functioning or self-awareness simultaneously with self-reported driving behaviors since this was not an objective of our study, but these would all be important aspects to address in future studies. Finally, a cross-sectional study cannot fully capture the temporal evolution of driving behaviors, and longitudinal studies are warranted to track changes in driving behaviors over time following a TBI.

CONCLUSIONS AND RECOMMENDATIONS FOR PRACTICE

In this study participants with TBI having passed a driving evaluation resumed driving at the same level as participants with TBI who did not undergo a driving evaluation and as non-injured controls, but they appeared to underestimate their risky driving behaviors. Self-awareness concerning driving skills should be fully assessed during off- and on-road assessment of driving fitness during rehabilitation (63–66). Close collaboration between driving evaluation professionals and rehabilitation teams should be encouraged to better understand the cognitive, behavioral and psychological/personality characteristics that may impact driving post-TBI in order to specifically target them during interventions, as well as to determine the best time to perform the driving evaluation (67). Furthermore, emphasis should be put on driving retraining (68) even for those individuals with TBI who successfully complete a driving evaluation. Future clinical research should target evaluation of on-road driving evaluation/retraining evidence-based practices, as well as systematic post-rehabilitation follow-up of individuals with TBI who have passed a driving evaluation, as well as those who were not targeted as needing a driving evaluation, but who may be considered at risk.

Based on the results of the current study, the critical review of the literature, and our clinical experience in different rehabilitation fields and more broadly in driving psychology, some clinical and policy recommendations are proposed:

- The finding that compared to pre-injury levels, individuals with TBI had significantly more demerit points post-rehabilitation compared to their pre-injury driving records has important public health implications. We recommend that during rehabilitation individuals with TBI be closely monitored regarding abilities and behaviors related to driving skills. Prevention measures such as mandatory training to increase their driving abilities as well as awareness of risks for road accidents and driving sanctions if they transgress road safety rules, could be systematically implemented even in individuals with TBI who have successfully undergone a driving evaluation process.
- As suggested by Deffenbacher et al. (57), interventions for angry drivers acknowledging that they may have anger-related difficulties could include psychoeducational and psychotherapeutic interventions. On the contrary, interventions for angry drivers who do not accept that they have a problem could include the readiness and motivation to address them and increasing awareness of their problems and risks (e.g., readiness enhancement interventions and motivational interviewing). Those interventions recommended for non-injured individuals could be adapted to individuals with TBI and be part of public policies to prevent negative driving-related outcomes.
- To date, there are no single measures or a combination of measures that will accurately predict who is and who is not a safe driver following a TBI (69). As such, driving evaluation professionals must ensure that they have performed a complete evidence-based assessment of their clients before they proceed to suggest accommodations, driving restrictions, or to stop driving. This should be done in close collaboration with interdisciplinary rehabilitation professionals involved in treating the person with a TBI.
- When available, driving simulators are a controlled and repeatable strategy to measure driver behaviors (70). However, more research is needed to justify their use in clinical practice for assessment and intervention purposes (70–72). But even

with normal neuropsychological results, clinicians must be aware that emotional and personality changes can also play a role in driving safety.

- Restricted licensing offers an alternative to license withdrawal in many North American jurisdictions and in Australia to help individuals in the transition to independent and safe driving allowing them to drive only under certain conditions (e.g.,driving in a specific geographical area), but more evidence is needed in the context of TBI (68).

AUTHOR CONTRIBUTIONS

MM, PD, and IG designed the study and conducted data collection. AM and MM conducted statistical analyses and drafted the manuscript. All authors reviewed the different iterations of the manuscript and approved the final version.

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Global Outcome Trajectories up to 10 Years After Moderate to Severe Traumatic Brain Injury

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Aims: Based on important predictors, global functional outcome after traumatic brain injury (TBI) may vary significantly over time. This study sought to: (1) describe changes in the Glasgow Outcome Scale–Extended (GOSE) score in survivors of moderate to severe TBI, (2) examine longitudinal GOSE trajectories up to 10 years after injury, and (3) investigate predictors of these trajectories based on socio-demographic and injury characteristics.

Methods: Socio-demographic and injury characteristics of 97 TBI survivors aged 16–55 years were recorded at baseline. GOSE was used as a measure of TBI-related global outcome and assessed at 1-, 2-, 5-, and 10-year follow-ups. Hierarchical linear models were used to examine global outcomes over time and whether those outcomes could be predicted by: time, time*time, sex, age, partner relationship status, education, employment pre-injury, occupation, cause of injury, acute Glasgow Coma Scale score, length of post-traumatic amnesia (PTA), CT findings, and Injury Severity Score (ISS), as well as the interactions between each of the significant predictors and time*time.

Results: Between 5- and 10-year follow-ups, 37% had deteriorated, 7% had improved, and 56% showed no change in global outcome. Better GOSE trajectories were predicted by male gender ($p = 0.013$), younger age ($p = 0.012$), employment at admission ($p = 0.012$), white collar occupation ($p = 0.014$), and shorter PTA length ($p = 0.001$). The time*time*occupation type interaction effect ($p = 0.001$) identified different trajectory slopes between survivors in white and blue collar occupations. The time*time*PTA interaction effect ($p = 0.023$) identified a more marked increase and subsequent decrease in functional level among survivors with longer PTA duration.

Conclusion: A larger proportion of survivors experienced deterioration in GOSE scores over time, supporting the concept of TBI as a chronic health condition. Younger age, pre-injury employment, and shorter PTA duration are important prognostic factors for better long-term global outcomes, supporting the existing literature, whereas male gender and white collar occupation are vaguer as prognostic factors. This information suggests that more intensive and tailored rehabilitation programs may be required to counteract a negative global outcome development in survivors with predicted worse outcome and to meet their long-term changing needs.

Keywords: brain injury, outcome assessment, GOSE, prospective studies, rehabilitation

INTRODUCTION

Traumatic brain injury (TBI) remains one of the main causes of life years lost due to disability or death (1, 2). Worldwide, an estimated 50 million people sustain TBI each year (1). Research over past decades has made it clear that TBI should be conceptualized as a chronic health condition as opposed to an acute time bound event, as it continues to evolve long after initial recovery (3, 4).

The level of disability and global neurological functional outcome following TBI is commonly measured with the Glasgow Outcome Scale (GOS) or its extended version (GOSE) (5, 6). Both summarize the overall impact of TBI on function, independence and participation. Currently, the GOSE is the recommended core global measurement in TBI research (7, 8). Several large-scale studies have found that about 50% of individuals achieve a favorable outcome (i.e., moderate disability or good recovery outcome) at 6 months after sustaining moderate to severe TBI (9, 10), while a favorable outcome was assessed in 42% of individuals 6 months after sustaining severe TBI (11). Ponsford et al. (12) assessed GOSE scores using a cross-sectional design approximately 10 years after complicated mild to severe TBI, and found that 52% of individuals had good recovery, 44% had moderate disability and 5% had severe disability.

Thus far, only a few studies have assessed GOSE trajectories over longer periods after TBI (e.g., over 5 years). Corrigan and Hammond (4) examined changes in GOSE score categories over four consecutive follow-ups up to 15 years after TBI with data from the Traumatic Brain Injury Model Systems (TBIMS) database (13) in the US, and found dynamic positive and negative changes in GOSE scores between the time points. A UK study (14) assessed changes in disability from 1 year to 5–7 years after mild to severe TBI, and found that 24% of survivors with moderate to severe disability had improved to good recovery, whereas 25% of survivors with good recovery deteriorated to disabled. A Norwegian study (15) followed up survivors of moderate to severe TBI longitudinally and found that GOSE scores remained stable across the first 5 years after injury. A Swedish study (16) reported no significant difference in GOS outcome between 1 year and 10–15 years in survivors after severe TBI; similarly, a recent Norwegian study (17) found stable global functioning between 10 and 20 years after moderate to severe TBI. These Scandinavian findings of stable levels of disability are contrary to the findings in two large TBIMS studies (18, 19) that reported initial improvement in functional status up to approximately 10 years after injury, followed by a peak and a decline in GOSE scores (i.e., increasing disability).

There is increasing evidence for the factors that predict functional outcome after TBI; age (10, 15, 16, 18–26), sex (20, 27), education (21, 28–30), pre-injury employment (15, 20, 28, 31), race (18, 32, 33), history of alcohol abuse prior to injury (20, 34), presence of intracranial lesions (25, 35–37), acute Glasgow Coma Scale (GCS) score (25, 37), duration of post-traumatic amnesia (PTA) (15, 29), duration of hospitalization and rehabilitation stays (18, 19), executive function and memory problems (14, 21, 29, 30, 38), and mood disorders (14, 21, 29, 34, 39, 40). However, the findings of the predictive power of these factors are mixed, partly due to methodological differences between the studies.

Our research group has published GOSE score trajectories up to 5 years after moderate to severe TBI (15). The present study is an extension with a 10-year follow-up after injury. TBI survivors may live for decades after their injury and a better understanding of long-term global outcome after moderate to severe TBI is needed. Delineating the relationships between socio-demographics and injury severity characteristics and functional outcome may yield valuable information on management, rehabilitation, and counseling for TBI survivors at risk for impaired recovery.

The specific study aims were:

1. To describe GOSE score changes up to 10 years after injury.
2. To assess the trajectories of global functioning in people with moderate to severe TBI at 1, 2, 5, and 10 years post-injury.
3. To investigate whether socio-demographics and injury severity characteristics can predict the trajectories of global functioning.

Based on results from our previous follow-up studies in the first 5 years (15) and 10–20 years after injury (17), we hypothesized that TBI-related global outcome would remain stable over the first 10 years after moderate to severe TBI, and that age, sex, pre-injury employment and injury severity characteristics such as PTA would be associated with functional outcome.

MATERIALS AND METHODS

Participants

The present study is a longitudinal cohort consisting of individuals with TBI who were admitted to the Trauma Referral Centre for the Southeast region of Norway from 2005 to 2007. The participants were assessed in the acute phase (baseline) and followed up at 1, 2, 5, and 10 years after injury. **The inclusion**

criteria were: (a) age 16–55 years, (b) admission with ICD-10 diagnosis S06.0-S06.9 within 24 h of injury, (c) moderate to severe TBI, classified by an acute GCS score of 3–12 (41) at admission or before intubation, and (d) residence in eastern Norway. **The exclusion criteria were:** (a) previous neurological disorders/injuries, (b) associated spinal cord injuries, (c) previously diagnosed severe psychiatric or substance abuse disorders, and (d) unknown address or incarceration.

In total, 133 people with TBI fulfilled the inclusion criteria. Of these, 24 died in the acute or post-acute phase, and four withdrew before the 1-year follow-up. One participant died and four dropped out of the study between 1 and 2 years. Between the 2- and 5-year follow-up, two participants died and four dropped out. Between the 5- and 10-year follow-up, 5 participants died and 12 dropped out, leaving 77 participants at the last follow-up. Altogether, 32 individuals died from baseline to 10-year follow-up, and these were excluded from the statistical analyses. The present study analyzed data from the surviving population with complete GOSE data at the 1-year follow-up ($n = 97$), with an attrition rate of 21% from the 1–10-year follow-up. A series of papers on functional outcome and health-related quality of life have previously been published based upon the same longitudinal cohort (15, 31, 42–51), please see Howe et al. (43) for a detailed flowchart of the follow-up process up to 10 years after injury.

Measures

In the present study, the dependent variable was the GOSE (6). The GOSE measures global outcomes (independence, employment, social and leisure activities, family and friendship, return to normal life) after TBI and divides individuals into the following outcome categories: 1 = dead, 2 = vegetative state, 3 = lower severe disability (i.e., complete dependence on others), 4 = upper severe disability (i.e., dependence on others, but can be on their own for 8 hours), 5 = lower moderate disability (living independently, not working or working at a lower level of performance/sheltered work), 6 = upper moderate disability (returning to previous work with adjustments), 7 = lower good recovery (almost back at full functional recovery; only minor physical or mental deficits), and 8 = upper good recovery (full functional recovery). The following independent variables (predictors) were used in the present study: Sex (male vs. female), age at time of injury (continuous, in years), relationship status at time of injury [partnered (married/cohabitant) vs. single], education at time of injury (continuous in years or categorical, i.e., $\leq$12 years vs. >12 years), employment status at time of injury (employed vs. unemployed), occupation type at time of injury [blue collar (physical work) vs. white collar (non-physical work/student)], acute GCS score (continuous, range 3–12), cause of injury (traffic accident vs. other), length of PTA (continuous, in number of days) as measured by the Galveston Orientation and Amnesia Test (GOAT) (52), computed tomography (CT) head Marshall scores [grading injury severity from I (no visible intracranial pathology) to VI (non-evacuated mass lesions)] (53) on the "worst" CT scan within the first 24 h of injury (i.e., the scan showing most extensive intracranial damage), and Injury Severity Score (ISS, continuous, ranges 1–75 [best to worst]) (54).

Procedure

Pre-injury and injury-related variables were extracted from medical records. At the 1-, 2-, 5- and 10-year follow-ups, the assessments of the participants including GOSE were most commonly performed by a physiatrist at the outpatient department. In some cases the assessments were completed by an ambulatory team originating from the outpatient department, or by phone interview, if requested by the participants. All participants provided written informed consent to take part in the study.

Statistical Analysis

Descriptive statistics were used to present socio-demographics and injury-related variables, and the results are presented as percentages and means with standard deviations (SD) or medians with interquartile range (IQR) as appropriate. GOSE score changes over time were also examined with descriptive statistics.

Hierarchical linear models (HLMs) were used to assess the trajectory of global function and examine baseline predictors of GOSE trajectory architecture across 1, 2, 5, and 10 years after injury. Full information maximum likelihood (FIML) estimation was used for handling missing data at the follow-ups, thus retaining all participants in the model ($n = 97$). A conditional (null) model was run first to determine whether there was sufficiently large clustering of GOSE score variance within participants to proceed with HLM. Unconditional growth (linear), quadratic, and cubic models were then run without predictors to determine the most accurate model for linear or polynomial architecture of GOSE scores over time.

Once the most accurate curvature model was identified, predictors were entered simultaneously as fixed effects into a HLM after being centered or given a reference point of 0, along with time and time*time (due to the selection of a quadratic trend of GOSE scores over time, outlined below). The first full model used a HLM to determine whether quadratic trajectories of GOSE scores across the four time points could be predicted by the socio-demographic and injury characteristics of time [coded as 0 (1 year), 1 (2 years), 4 (5 years), or 9 (10 years) to reflect actual spacing between time points], time*time, sex (1 = woman, 0 = man), age, partner relationship status (1 = partnered, 0 = single), education, employment at time of injury (1 = employed, 0 = unemployed), occupation type (1 = white collar, 0 = blue collar), GCS score, cause of injury (1 = motor vehicle, 0 = not motor vehicle), length of PTA (days), CT severity score, and ISS. A final HLM included the previously significant predictors from the first full model, time, time*time, and the interaction terms between time*time and the previously significant predictors.

RESULTS

The mean age of the 97 participants at the time of injury was 30.3 years (SD = 10.8); 78% of the participants were male. The mean GCS score at hospital admission was 7.2 (SD = 3.2); the mean PTA was 26 days (SD = 30). The mean ISS score was 30.0 (SD = 13.6). Two-thirds of the participants had severe TBI according to GCS score, whereas about half of the participants were classified as having more severe intracranial

TABLE 1 | Socio-demographics at time of injury and injury characteristics of 97 survivors.

Variable	*n* (%)	Total *n*
Age at injury		97
Mean (SD)	30.3 (10.8)	
Sex		97
Male	76 (78.4)	
Female	21 (21.6)	
Relationship status		97
Partnered	28 (28.9)	
Single	69 (71.1)	
Education level		96
≤12 years	54 (56.3)	
>12 years	42 (43.7)	
Employment status		97
Employed	80 (82.5)	
Unemployed	17 (17.5)	
Occupation type		97
Blue collar	46 (47.4)	
White collar	51 (52.6)	
Injury cause		97
Traffic accident	58 (59.8)	
Other	39 (40.2)	
Glasgow coma scale score		97
Mean (SD)	7.2 (3.2)	
Moderate (9–12)	32 (33.0)	
Severe (3–8)	65 (67.0)	
Post-traumatic amnesia duration		91
Days, Mean (SD)	26.0 (30.0)	
Median (IQR)	18.0 (2–38)	
CT Head Marshall Score		97
Mean (SD)	2.6 (1.1)	
Score 1-2	46 (47.4)	
Score 3+	51 (52.6)	
Injury Severity Score		97
Mean (SD)	30.0 (13.6)	
Total acute length of stay		97
Days, mean (SD)	29.0 (25.0)	
In-patient rehab. length of stay		71*
Days, Mean (SD)	59.0 (37.0)	

**In-patient rehabilitation was received by 71 individuals in total (mean length of stay is only calculated for those receiving it).*

injury according to the CT head Marshall Score. At time of injury, 83% of the participants were employed and 53% had white collar occupations. **Table 1** presents the socio-demographic and injury-related characteristics.

GOSE Score Changes Over Time

Figure 1 shows the distribution of patient frequency between GOSE score categories. The proportion of participants with upper good recovery increased over time from 10 to 23% from 1 year to 10 years after injury, whereas the proportion of participants in the lower good recovery group decreased markedly from 29% to 8%. The trend between the moderate disability categories was the opposite, with the proportion of participants in the upper moderate disability group remaining stable at 37–40% from 1 year to 5 years before decreasing to 25% at the 10-year follow-up, whereas the proportion of participants in the lower moderate disability group approximately doubled from 14 to 31%. The severe disability groups remained relatively stable before there was an increase in the upper severe disability group at the 10-year follow-up.

Table 2 shows the changes in GOSE score categories between the 1- and 2-year, 2- and 5-year, and 5- and 10-year follow-up. The majority of participants had stable GOSE scores between each time point, with 57–67% showing no change. In the 1- to 2-year and 2- to 5-year follow-ups, 21–22% of participants had an increase of one GOSE category, whereas this dropped to 7% in the 5- to 10-year follow-up. Conversely, only 9–13% of participants had a decrease in one category between the 1- to 2-year and 2- to 5-year follow-up, whereas 30% had a decrease between the 5- to 10-year follow-up.

In total, of the 77 participants with GOSE data at both 1- and 10-year follow-up, 77% had changed GOSE scores between follow-ups (across all time points). Of those with the same GOSE score at 1 and 10 years ($n = 28$), more than one-third had a dynamic GOSE score change between the time points. When only looking at GOSE score changes between the 1- and 10-year follow-up, 26% of participants had increased one, two, or three GOSE categories in terms of function, 36% showed no change, whereas 38% decreased one to two categories (data not shown).

Unconditional Model and Unconditional Growth Model

The unconditional model yielded a statistically significant estimated participant variance of 1.10 (Wald $Z = 5.71$, $p < 0.001$), and a statistically significant estimated residual variance of 0.83 (Wald $Z = 11.43$, $p < 0.001$). The intraclass correlation coefficient was 0.57, indicating that approximately 57% of the total variance of GOSE scores was associated with participant grouping and that the assumption of independence was violated. This suggests there was sufficiently large clustering of GOSE score variance within participants to proceed with a HLM. The unconditional model was then run separately with the successive additions time, quadratic time, and cubic time to determine the shape of the best-fitting curve of the GOSE over time (**Table 3**), suggesting that a quadratic trajectory best fit the GOSE over time.

Full HLM

The full HLM examined whether socio-demographic and injury characteristics at baseline could predict the quadratic trajectories of GOSE scores over time. **Table 4** shows all statistically significant and non-significant fixed effects from the full HLM and their b-weights, *p*-values, and 95% confidence intervals. The GOSE scores showed a significant quadratic trend over time, conforming to an initial increase and then decrease. Sex, age, employment at time of injury, occupation type, and length of

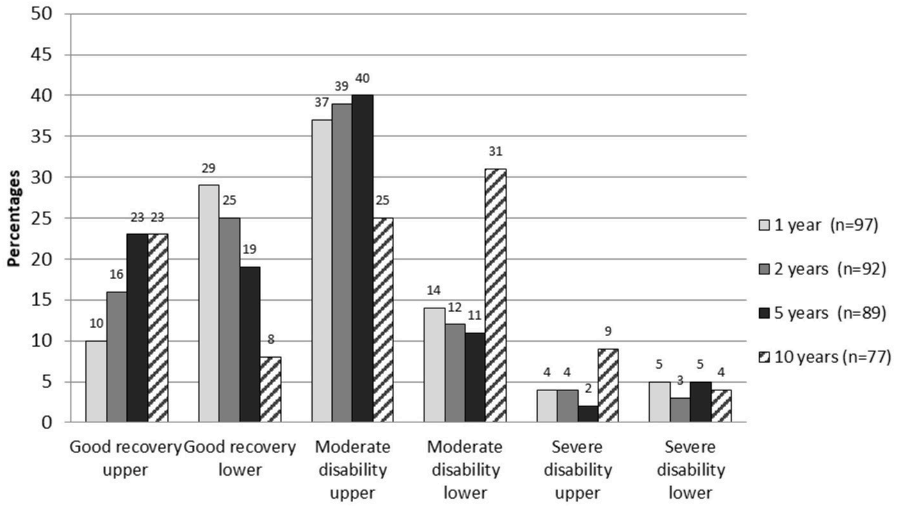

FIGURE 1 | GOSE score distribution at 1-, 2-, 5-, and 10-year follow-up.

TABLE 2 | Changes in Glasgow Outcome Scale-Extended (GOSE) categories (in percentages) between time-points.

GOSE change	1–2 years (*n* = 92)	2–5 years (*n* = 86)	5–10 years (*n* = 76)
Increased 2 categories	2	2	0
Increased 1 category	22	21	7
No change	67	62	56
Decreased 1 category	9	13	30
Decreased 2 categories	0	2	7

TABLE 3 | Model fit for GOSE trajectories over time.

Model	-2 Log Likelihood
Unconditional growth model	1049.64
Quadratic	1022.20*
Cubic	1021.96

Criticalχ^2 value for significant difference at $\alpha = 0.05$ is ≥ 3.841 drop from the previous model (= significant improvement).*

PTA yielded statistically significant effects on the participants' GOSE trajectories. Men had higher GOSE quadratic trajectories across the four time points than women (**Figure 2**) ($p = 0.013$). Younger participants had higher GOSE quadratic trajectories than older participants (**Figure 3**) ($p = 0.012$). Participants who had been employed at time of injury had higher GOSE quadratic trajectories than those who had been unemployed (**Figure 4**) ($p = 0.012$). Participants in a white collar profession had higher GOSE quadratic trajectories than those in a blue collar profession (**Figure 5**) ($p = 0.014$). Finally, participants with a shorter PTA length had higher GOSE quadratic trajectories than those with a longer PTA duration (**Figure 6**) ($p = 0.001$).

Final HLM With Quadratic Time Interactions

The final HLM examined whether the previously significant predictors, as well as their interactions with quadratic time, could predict the quadratic trajectories of the GOSE scores. **Table 5** shows all statistically significant and non-significant fixed effects from the final HLM and their b-weights, *p*-values, and 95% confidence intervals, although only the significant interaction terms will be focused on for interpretation. The significant time*time*occupation type interaction effect suggested that participants in a white collar profession tended to have a slightly increasing trajectory over the first 5 years, which curved back toward 1-year levels at 10 years (**Figure 5**). However, participants in a blue collar profession had a smaller increase in GOSE scores during the first 5 years, but a dramatic decrease in GOSE scores at 10 years, ending nearly a full point below their scores at the 1-year follow-up. The significant time*time*PTA interaction suggested that participants with shorter PTA duration had a slightly increased and then decreased trajectory over the 10 years, with GOSE scores at the final follow-up being somewhat lower than the scores at the 1-year follow-up (**Figure 6**). However, participants with longer PTA duration tended to have a sharper increase but then a more dramatic decrease in GOSE scores over the 10 years, ending with GOSE scores nearly half a point below their 1-year scores.

DISCUSSION

This study is one of a few prospective studies to investigate the changes and predictors of global functioning in survivors of moderate to severe TBI over the first 10 years after injury. First, the distribution of GOSE categories over time showed dynamic changes, with improvement and deterioration over time. From the 5 to 10-year follow-up, approximately 7% of survivors improved one category, 56% showed no change, while

TABLE 4 | Socio-demographic and injury predictors of GOSE trajectories across 1, 2, 5, and 10 years after injury.

Predictor	b-weight	*SE*	*p*-value	95% confidence interval	
				Lower bound	Upper bound
Intercept	5.90***	0.23	<0.0001	5.45	6.36
Time	0.016**	0.06	0.007	0.04	0.27
Sex (1 = woman, 0 = man)	−0.46*	0.18	0.013	−0.82	−0.10
Age	−0.02*	0.01	0.012	−0.04	−0.01
Relationship status (1 = partnered, 0 = single)	0.14	0.20	0.475	−0.25	0.53
Education	0.05	0.10	0.619	−0.15	0.25
Employment (1 = employed, 0 = unemployed)	0.51*	0.20	0.012	0.11	0.90
Occupation type (1 = white collar, 0 = blue collar)	0.43*	0.17	0.014	0.09	0.78
Glasgow coma scale score	0.02	0.03	0.383	−0.03	0.08
Cause of injury (1 = motor vehicle, 0 = not motor vehicle)	−0.29	0.17	0.099	−0.63	0.06
Post-traumatic amnesia	−0.01**	0.00	0.001	−0.02	0.00
CT severity score	−0.13	0.07	0.084	−0.28	0.02
Injury severity score	−0.01	0.01	0.405	−0.02	0.01
Time*time	−0.02***	0.01	<0.0001	−0.03	−0.01

Full hierarchical model. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.0001$.

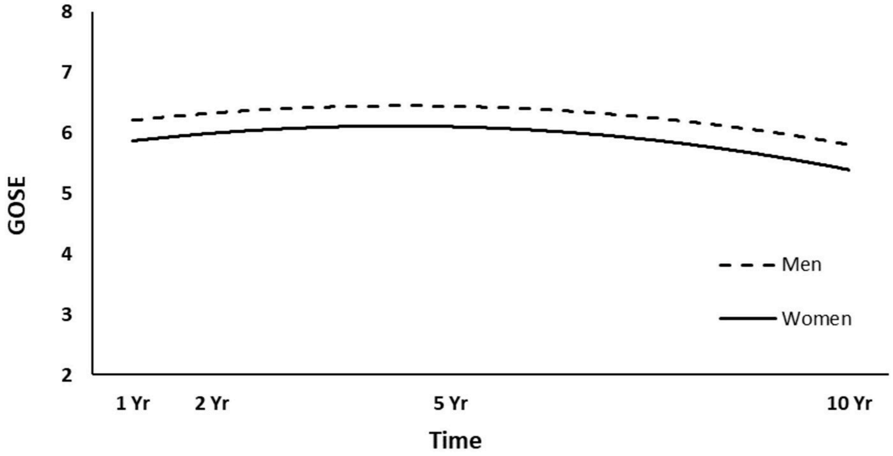

FIGURE 2 | Main effect of sex on GOSE trajectories.

37% worsened one or two categories. Second, trajectory analysis using HLM suggested different global outcome trajectories within the cohort of survivors. Third, predictor analysis determined that sex, age, employment at time of injury, occupation type, and length of PTA yielded statistically significant effects on participants' GOSE trajectories. The findings provide insight in which TBI survivors face an increased risk of deterioration of global functioning over time, with the possibility of initiating tailored rehabilitation programs to attempt to counteract this development and to meet the long-term changing needs of this population.

When assessing changes in GOSE score categories between three consecutive follow-ups in the present study, there was a clear trend for more negative change toward the 10-year follow-up. Corrigan and Hammond (4) studied changes in GOSE score categories over four consecutive follow-ups (1–2, 2–5, 5–10, and 10–15 years after TBI). When looking at the development in GOSE scores in the 5–10-year follow-ups (n = 796), 42% of participants showed no change in GOSE score, whereas 24% improved one or two categories, and 34% deteriorated one or two categories. Compared to the present study, Corrigan and Hammond found a smaller proportion of participants with no change and a higher proportion of participants with improvement. However, similar to our results, a larger proportion of the survivors tended to experience deterioration in GOSE scores over time, supporting the concept of TBI as a chronic health condition (3).

McMillan et al. (39) followed survivors at 1, 5–7, and 12–14 years after mild to severe TBI (n = 87), where the GOSE score from 1 year to 12–14 years improved in 34% of survivors,

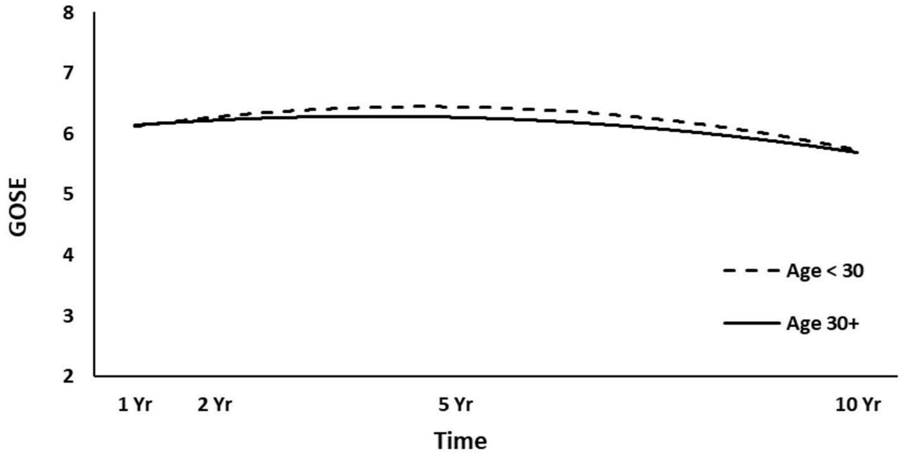

FIGURE 3 | Main effect of age (dichotomized at mean value) on GOSE trajectories.

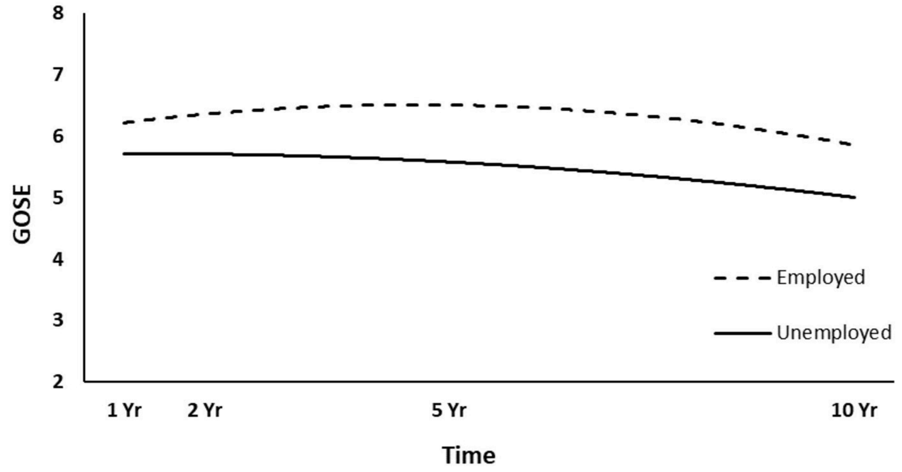

FIGURE 4 | Main effect of employment at time of injury on GOSE trajectories.

remained the same in 32%, and worsened in 34%. These results are in line with our results from the 1 to 10-year follow-ups. However, they found that 23% of participants improved between the 5–7- and 12–14-year follow-ups, which is a much higher proportion compared to our study (7% from 5 to 10-year follow-up). Methodological differences between the two studies probably contributed to this discrepancy, where the study by McMillan have a high risk of selection bias due to significant drop out over time (*n* = 475 survivors assessed at 1-year follow-up, *n* = 87 survivors assessed at 12–14 years follow-up). In addition, a higher proportion of survivors with positive change can be expected in a study sample that included mild TBI. Andersson et al. (16) followed 61 survivors after severe TBI at 1 year and 10–15 years after injury with a stable GOS score between the time points, but reported that, in total, 15% of survivors had improved GOS scores, 55% showed no change, and 30% deteriorated. The more homogenous study sample of severe TBI (i.e., all requiring intracranial monitoring and artificial ventilation), as well as use of the GOS with fewer categories could perhaps explain a more stable functional outcome and less improvement over time as compared to our results.

The participants in the upper moderate disability and lower good recovery groups (GOSE score 6 and 7) had the largest negative change in GOSE scores from the 1- to 10-year follow-up. Our previous study on self-reported healthcare needs in survivors of moderate to severe TBI (49) found that survivors with GOSE scores of 6–8 (i.e., less severe disability) reported more unmet needs than survivors with GOSE scores of 2–5 (i.e., more severe disability) (38 vs. 13%). It was discussed that those with fewer problems may be more troubled by their problems and therefore report higher unmet needs, or perhaps this group is less prioritized for receiving healthcare services due to the assessed better outcome. We can only speculate whether the lack of healthcare services contributes to deterioration over time in this group.

Based on our previous studies (15, 17), we hypothesized that TBI-related global outcome would remain stable over the first 10 years after injury. Contrary to our hypothesis, the HLM

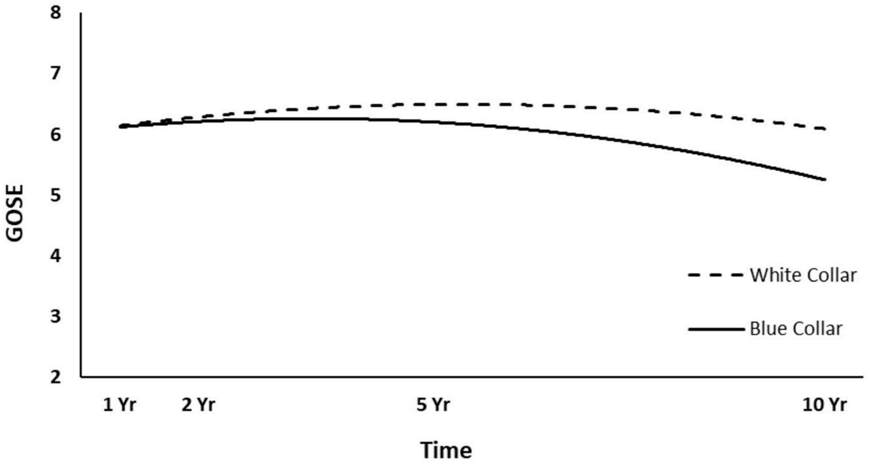

FIGURE 5 | Main effect and quadratic time interaction effect of occupation type on GOSE trajectories.

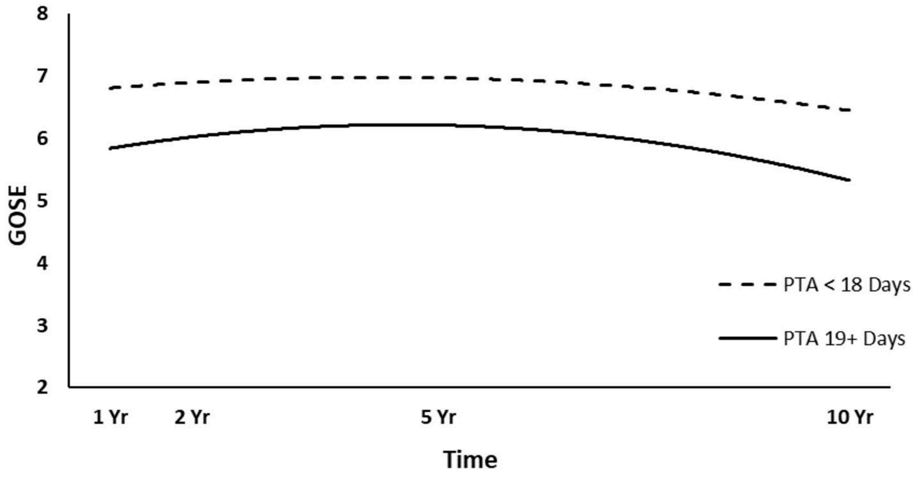

FIGURE 6 | Main effect and quadratic time interaction effect of post-traumatic amnesia (PTA) duration (dichotomized at median value) on GOSE trajectories.

of the quadratic GOSE score trajectories showed a significant change over time, with an initial increase and then decrease in GOSE scores up to 10 years after injury. These findings are partly consistent with two larger US studies looking at GOSE trajectories up to 20 years after TBI (18, 19), which found initial improvement in functional status before a peak, and a decline in GOSE scores. However, the decline started after the 10-year follow-up. It is possible that the socio-demographic and injury-related differences between study populations can explain these results; nonetheless, we could not make a closer comparison due to the limited reporting of such data in the US studies.

We found that TBI survivors who were male, younger, employed at time of injury, in a white collar occupation and with a shorter PTA duration (i.e., lower injury severity), had significantly higher global functioning across 1, 2, 5, and 10 years after moderate to severe TBI. Thus, the results are in agreement with our hypothesis.

Contrary to previous long-term studies (18, 19) and previous results reported from the present study sample (15), we found in the present study that men experience better functional trajectories up to 10 years after TBI. This is in line with a meta-analysis that found poorer outcomes in women for 85% of the measured outcome variables, including disability, after mild to severe TBI (27). Another review found inconclusive evidence of the gender effect on disability outcome, but most studies reported worse outcomes for women (20). Taken together, gender differences remain understudied and poorly understood in relation to TBI outcomes (55). The finding of better GOSE probability trajectories for younger survivors is consistent with a broad literature, which reports significantly better global functioning after TBI in younger survivors (15, 16, 18–21, 26). Return to work at different levels is captured through the representation of GOSE categories 5–8, from being able to work only with large adjustments/sheltered work to full functional recovery. A recent study of the present cohort has shown stable employment trajectories over 1, 2, 5, and 10 years after injury, with approximately half of the survivors returning to work (43). Numerous studies have shown that employment prior to

TABLE 5 | Previously significant predictors and quadratic time interactions on GOSE trajectories across 1, 2, 5, and 10 years after injury.

Predictor	b-weight	*SE*	*p*-value	95% confidence interval	
				Lower bound	Upper bound
Intercept	5.86	0.22	<0.0001	5.43	6.29
Time	0.17**	0.06	0.003	0.06	0.28
Sex (1 = woman, 0 = man)	−0.34	0.20	0.086	−0.73	0.05
Age	−0.01	0.01	0.095	−0.03	0.00
Employment (1 = employed, 0 = unemployed)	0.52*	0.22	0.018	0.09	0.95
Occupation type (1 = white collar, 0 = blue collar)	0.19	0.17	0.277	−0.15	0.53
Post-traumatic amnesia	−0.02***	0.00	<0.0001	−0.02	−0.01
Time*time	−0.03***	0.01	<0.0001	−0.04	−0.01
Time*time*sex	−0.01	0.00	0.194	−0.01	0.00
Time*time*age	0.00	0.00	0.597	0.00	0.00
Time*time*employment	0.00	0.00	0.982	−0.01	0.01
Time*time*occupation type	0.01**	0.00	0.001	0.00	0.02
Time*time*post-traumatic amnesia	0.00*	0.00	0.023	0.00	0.00

Final hierarchical model. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.0001$.

injury is a strong predictor of return to work after moderate to severe TBI (46, 56, 57), which implies achieving a favorable outcome with regards to global function. In line with the present results, several studies have demonstrated a significant association between pre-injury employment and disability after TBI (15, 20, 31, 58). White collar occupation (i.e., professional, managerial, or administrative work) at the time of injury was a significant predictor of better GOSE trajectories up to 10 years after TBI. Interestingly, previous studies have not demonstrated this association, but it has been found to be a predictor of return to work (46, 59). In line with previous studies, lower injury severity (i.e., shorter PTA duration) was a significant predictor of better functioning trajectories at 1, 2, 5, and 10 years post-TBI (15, 29).

LIMITATIONS AND FUTURE DIRECTIONS

The present study has several limitations that should be acknowledged when interpreting the results. The inclusion criteria included survivors of moderate to severe TBI and aged 16–55 years; therefore, the results cannot be readily generalized to individuals with mild TBI or to individuals outside this age range. The participants were recruited through the Trauma Referral Centre and represent a mixed population with regards to the type and extent of inpatient rehabilitation received, and should therefore be representative of a broader range of patients than, for example, those in the TBIMS studies. Previous studies have hypothesized that trajectories of disability in elderly populations (aged >65 years) could differ from that of younger adult survivors of TBI (26), but we did not include that age group in this study.

The present study sample is small, and over time there has been an inevitable loss to follow-up. However, the attrition rate of 21% in the 1–10-year follow-up is low compared to that of other studies (13). The descriptive GOSE score changes should be interpreted with caution due to the missing data points and risk of selection bias. However, the HLM handles missing data well, and the longitudinal design with four follow-up time points (i.e., 388 observations) renders the trajectory analysis much stronger with regards to statistical power.

To sum up, further research is needed to verify the present study findings, preferentially through international collaboration to establish standardized research methodology and thereby generalizable knowledge on long-term functional outcome following TBI. This can for example be accomplished through multinational clinical TBI trials. Future studies should also incorporate a broader set of variables, such as physical, psychological, and cognitive functioning; personal traits; use of healthcare and rehabilitation services; as well as psychosocial support and lifestyle factors.

CONCLUSIONS

This study aids understanding of the natural history of recovery following moderate to severe TBI by highlighting the trajectories of global functioning from the 1-year to 10-year follow-up, and examining predictors of better GOSE outcomes. The results suggests that more intensive and tailored rehabilitation programs may be required to counteract a negative global outcome development in survivors of older age, those unemployed at the time of injury and those with a longer PTA duration, as well as to address the long-term changing needs of this population.

DATA AVAILABILITY

The dataset for this study will not be made publicly available. The dataset is not anonymous and cannot be shared publicly according to the Norwegian law on research ethics and medical research. The dataset can be reviewed on the grounds of Oslo University Hospital upon request, if considered appropriate and approved by the Regional Committees for Medical and Health Research Ethics (REC).

ETHICS STATEMENT

The present study was conducted in accordance with the recommendations of the Norwegian law on research ethics and medical research. The protocol was approved by the Regional Committee for Medical and Health Research Ethics, East Norway, and the Norwegian Data Inspectorate. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

MF, CR, SS, and NA contributed to the study design, data acquisition, analysis, interpretation, drafting, and finalizing of the manuscript. PP contributed to the analysis, interpretation, drafting, and finalizing of the manuscript. TH, SB, JL, and JA-L contributed to the data interpretation, drafting, and finalizing of the manuscript.

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Employment Status Among U.S. Military Veterans With Traumatic Brain Injury: Mediation Analyses and the Goal of Tertiary Prevention

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For most individuals with traumatic brain injury (TBI), the ability to work is crucial to financial and psychological well-being. TBI produces a wide range of cognitive, physical, emotional, and interpersonal impairments that may undermine the ability to work. Employment is therefore a primary goal of TBI rehabilitation and has been the focus of extensive research. Although this literature has identified predictors of employment outcomes, few studies have examined the mechanisms that underlie these associations. Mediation analysis can identify these mechanisms, provide a more nuanced view of how predictors jointly affect rehabilitation outcomes, and identify predictors that, if treatable conditions, could be useful targets for tertiary prevention. Such efforts are aimed at reducing long-term impairments, disability, or suffering resulting from the injury. The study sample comprised 83 U.S. military veterans with TBI who had participated in a larger rehabilitation study and were interviewed in their homes. Bivariate tests revealed significant associations of employment with pain, cognitive functioning, self-rated health, depressive symptoms and physical functioning; the latter variable was operationalized in two ways—using the Patient Competency Rating Scale and the SF–36V physical functioning subscales. Because these physical functioning measures were highly intercorrelated ($r = 0.69$, $p < 0.0001$), separate regression models were conducted. In the hierarchical binary logistic regression models, predictors were entered in order of modifiability, with comorbidities (pain) entered in block 1, physical health/functioning sequelae in block 2, and depressive symptoms in block 3. In the regression using the SF-36V measure of physical functioning, pain's effect was mediated by the physical functioning/health predictors, with only physical functioning emerging as significant, but this effect was itself mediated by depressive symptoms. In the regression using the PCRS physical-function measure, only depressive symptoms emerged as a mediator of other effects. Findings underscore the central role of depression in the employment status of veterans with TBI, suggesting that negative effects of other problems/limitations could be mitigated by more effective treatment of depression. Thus, for many with chronic TBI who live with vocational limitations, outcomes may improve with lower depression. Findings argue for the wider use of mediation approaches in TBI research as a means of identifying targets for tertiary prevention of poor outcomes.

Keywords: traumatic brain injury, military veterans, employment, depression, physical functioning, pain, tertiary care

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INTRODUCTION

Traumatic brain injury (TBI) may produce a wide range of cognitive, emotional, interpersonal, and physical sequelae, (1–7) any of which may impair the ability to work. An important goal of rehabilitation for most individuals with TBI, work is crucial to financial and psychological well-being (8–10). The importance of employment is attested to by an extensive research literature documenting the impact of employment problems and identifying predictors of employment status, return to work (RTW), and employment stability (11–13).

Most studies of predictors of employment outcomes have used some form of multiple regression to identify those that contribute independently. Certain variables have emerged fairly consistently as predictors of employment: younger age at injury (14, 15), White race and non-Hispanic ethnicity (16–18), higher educational level (19), pre-injury unemployment (20), higher pre-injury occupational status (12, 14, 15); lower injury severity (15, 21, 22); higher Glasgow Coma Scale scores (19); higher cognitive function (12, 19, 23), everyday functioning (which may include physical, cognitive, emotional, interpersonal, or other dimensions) (11, 12, 24–27); and lower depression (7, 14, 28–38). Relatively neglected have been closer examinations of the interrelationships among these variables using mediation analyses. The use of mediation methods such as hierarchical multiple regression or structural equation modeling can provide a more nuanced view of how predictors jointly affect employment outcomes by identifying the mechanisms that underlie predictors' associations with employment outcomes (39). A mediator is an intervening variable that explains the reason for a relationship between an independent and dependent variable. It "carries the effect," indicating that an independent variable leads to a change in the mediator variable, which in turn leads to a change in the dependent variable (40).

Findings from mediation analyses can have practical implications for clinical practice, especially when the mediators represent modifiable conditions. These implications relate especially to tertiary prevention of TBI outcomes. Whereas primary prevention concerns preventing injury or disease, and secondary prevention concerns detecting them in their earliest stages and intervening to slow or stop their progression, the aim of tertiary prevention is to reduce long-term impairments, disability, and suffering resulting from them (41). Tertiary prevention efforts strive to soften the impact of an ongoing illness or injury that has lasting effects. Focusing on strategies to manage long-term health problems, tertiary prevention commonly includes chronic disease self-management programs and vocational rehabilitation programs (42).

Tertiary prevention has received relatively little research attention in TBI rehabilitation, which has overwhelmingly focused on its early post-injury phases (43–45). Yet, TBI sequelae often persist for years, and TBI is increasingly viewed as a chronic illness (20, 46–53). Its sequelae may undermine quality of life, community integration, and cognitive, emotional, and vocational functioning. Interventions for the chronic stage, after symptoms have stabilized, have been relatively neglected, leaving many individuals to deal with chronic TBI symptoms on their own (54). Therefore, tertiary prevention should be an important focus for TBI.

A treatable condition that is identified as a mediator of other effects may be a promising target for intervention efforts, because even if the predictor whose effect is mediated does not itself improve, treating the mediating condition may improve long-term outcomes. For example, the finding that depressive symptoms mediate the effect of post-traumatic stress disorder (PTSD) on community reintegration (55) would suggest that, even when PTSD has remediated as much as possible, community reintegration could be further improved by treating the depression. This is a tertiary prevention strategy.

Mediation analyses may therefore help identify targets for tertiary prevention efforts. To be a target for tertiary prevention, a predictor would have to represent a treatable condition and be shown to mediate effects of predictors entered previously. Thus, if a predictor is found to attenuate the effect of a previously-significant variable on an outcome, that mediating predictor may serve as a worthwhile rehabilitation focus. An analysis to test mediation would therefore order the variables' entry by degree of modifiability. Background characteristics like TBI severity and time post injury, would be entered first. Comorbidities, which are also background characteristics and may or may not be modifiable, would be entered next. Prominent among these would be PTSD (56, 57) and pain (57), both prevalent in veteran populations and highly comorbid with each other and with TBI. Entered next would be TBI sequelae. These commonly include limitations in cognitive, physical, emotional, and interpersonal functioning; and symptoms such as tinnitus and photosensitivity; and psychiatric disorders. Because psychiatric disorders are likely to be distinct from physical sequelae, these would be entered in a separate step.

Among psychiatric sequelae of TBI, depression is the most common and often has serious consequences for persons with TBI (35). It can interfere with motivation, diminish the ability to think or concentrate, produce feelings of pessimism and futility, and cause fatigue, loss of energy, and other somatic symptoms (53)—symptoms that can impair the ability to work. Depression has also been shown to mediate effects of other predictors on important outcomes in TBI, as mentioned earlier, mediating effects of both physical functioning and PTSD on community reintegration (CR) (defined as the extent to which the individual participates in activities with family, friends, and community) (58). Depression also mediates effects of insomnia on suicide risk among military veterans with or without TBI (59). In other (non-TBI) clinical populations, depression has been shown to mediate effects of severity, pain, or other predictors on rehabilitation outcomes such as functioning, quality of life, and community integration (60–63). Yet, depression is highly treatable (64). Among TBI patients, the most common depression treatments have been medication, especially the selective serotonin reuptake inhibitors (65–67), and cognitive behavioral therapy (CBT) (68–72). These considerations would argue for an analytic strategy of entering the depression variable separately from physical health and functioning in mediation models.

The present study examined predictors of employment status in a group of U.S. military veterans with TBI. These were outpatients at a U.S. Veteran Affairs medical rehabilitation clinic. Military TBI is known to differ from TBI in civilian populations in several respects. Multiple TBIs, high-energy explosives, and blast injuries are more common in military TBI (73). In addition, combat injuries are less likely to be diagnosed promptly and more likely to rely on self-reports (74). These features complicate efforts to characterize the severity of individual injuries, as might be done routinely after a civilian TBI event. Emotional distress tends to be greater in military TBI and comorbid mental health symptoms and conditions more prevalent. High rates of comorbidity among TBI, PTSD, and depression and their overlapping signs and symptoms complicate attribution to TBI or PTSD (75). Service members returning from military deployment may have more difficulty with community reintegration (56, 76).

In addition, within military TBI, a further distinction can be drawn between combat- and noncombat-related TBIs. In non-combat TBIs, mechanisms of injury such as vehicular crashes and falls may be similar to those in a civilian population (although crashes and falls also occur during combat). But most study participants had sustained multiple TBIs, some during combat (including many blast injuries) and others in non-combat situations. These consideration complicate efforts to classify TBI mechanisms.

Veterans in the present study had predominantly mild TBI (mTBI) with persistent post-concussive symptoms or mild-moderate TBI, and in this respect the study contrasts with most previous studies, which have tended to study more severe TBI. Yet mTBI accounts for more than half of cases worldwide (77), and mild to moderate TBI constitutes 82.7 percent of cases (78). Within the U.S., mTBI represents 80–90 percent (79). MTBI causes long-term mental and physical health consequences in a sizable minority of patients (80–83). A 2012 VA systematic review on complications of mTBI in veterans and military personnel estimated that 10–20 percent experience ongoing post-concussive symptoms (84).

The present study investigated potential mediation of predictors' effects on employment status. Hierarchical binary logistic multiple regression was used, with the order of entry determined by modifiability from least to most. The purpose of testing for mediation was to identify treatable conditions as potential targets for rehabilitation, especially for tertiary prevention.

The study was innovative in several respects. It used a mediation approach to seek targets for rehabilitation efforts toward tertiary prevention goals. It also utilized a less severely injured sample compared to most studies of employment outcomes and a military veteran population, who are also understudied in the area of the employment outcomes.

METHODS

Design

This was a secondary analysis of data collected in a randomized controlled trial that evaluated the efficacy of an in-home intervention (the Veterans In-home Program) for U.S. military veterans with TBI and their family members (55, 85). Data reported in the present study were collected during the baseline interview with veterans, prior to randomization.

Sample

Study participants were 83 veterans with TBI recruited from the Corporal Michael J. Crescenz Veterans Affairs (VA) Medical Center outpatient Rehabilitation Medicine Service. Since 2017, the VA has screened veterans of the Afghan and Iraq wars for TBI, evaluated those screening positive, and referred them to the Rehabilitation Medical Service. In addition, veterans from earlier war cohorts may be referred to this service by primary care, psychiatry, and other specialty providers. All study participants had recently received a TBI evaluation and TBI diagnosis through this service and were reporting current TBI-related symptoms (All had been screened for PTSD as well.). TBI etiology could be combat (e.g., blast exposure) or non-combat events such as vehicular crashes, falls, or equipment accidents, as explained above. Study participants were recruited using a letter of invitation mailed to eligible veterans, followed by a phone call that further described the study and confirmed the veteran's study eligibility, and determined his/her willingness to participate. Inclusion criteria included residence in the Philadelphia, Pennsylvania metropolitan region, diagnosis of TBI at the Polytrauma Program, post-deployment from the Vietnam War era to the present, ability to speak English, meeting VA Polytrauma Systems of Care criteria for TBI (86), and having a family member or partner living with him/her or living within close proximity and willing to participate in the study.

Measures

Sociodemographic Characteristics

The interview provided information on veterans' age, race, sex, Hispanic ethnicity, religious affiliation, financial difficulty (87), years of education, marital status, number of years married, number of children, and employment status. Because only five veterans were found to be employed part-time, employment status was defined as employed part- or full-time vs. not employed. No one had voluntarily retired.

Military and Injury-Related Characteristics

Electronic medical records from the VA Computerized Patient Record System (CPRS) provided background information augmenting interview data. This information encompassed the veteran's war cohort, number of years since most recent TBI (time post injury), source of injury, number of TBIs, and comorbidities (posttraumatic stress disorder [PTSD], pain, tinnitus, and photosensitivity). PTSD was defined as the presence or absence of a PTSD diagnosis documented as active in CPRS during the study period. All U.S. veterans receiving services at the medical rehabilitation clinic are screened for PTSD.

TBI severity was determined using the VA/DOD Clinical Guidelines for Management of Concussion/Mild Traumatic Brain Injury (mTBI) (86). A physician with rehabilitation medicine expertise (K.R.) reviewed the data in the electronic records to determine TBI severity. The diagnosis of TBI in these military personnel was based on several factors, including exposure to one of several events that could induce cerebral damage, the persistence of clinical symptoms and signs indicating that a brain injury may have occurred, and findings on brain imaging, either computerized tomography or brain MRI. As expected in TBIs classified in the mild and mild-to-moderate ranges of severity, brain imaging often can be reported as having no structural damage. But this does not preclude the diagnosis of TBI. For analytic purposes, severity was dichotomized into mild vs. moderate to severe.

Health and Functioning: Short Form Health Survey-36 Veteran Version (SF-36V)

The SF-36 is widely used for monitoring and assessing care outcomes in adult patients (88). It has been modified for use in VA ambulatory care patient populations (the SF-36V) (89, 90) and has demonstrated strong reliability and validity. The SF-36V consists of eight physical and mental health concepts. The present study utilized only the physical health/functioning domains: physical functioning limitations (e.g., limitations in lifting groceries), pain intensity, extent of pain's interference with everyday functioning, and self-rated health.

Pain

Pain is measured in terms of intensity and extent of interference with normal work. The intensity question uses a 6-point scale, from 0 (none) to 5 (severe), and the interference question uses a 5-point scale, from 0 (not at all) to 4 (extremely). Therefore, raw scores were converted to z-scores. Because the two pain items were highly correlated ($r = 0.76$, $p < 0.0001$), a mean score was computed and used as a pain index (Cronbach's alpha = 0.86). Higher scores indicate worse pain.

Physical Functioning

The physical functioning subscale assessed extent of limitations in 10 activities, each item followed by a 3-point response format from 0 (not at all limited) to 2 (limited a lot). Thus, higher scores indicate worse functioning. Cronbach's alpha for the SF-36V physical functioning subscale was 0.90 for this sample.

Self-Rated Health (SRH)

The SF-36V includes six items relating to SRH—overall health now ("In general, would you say your health is excellent, very good, good, fair or poor?"), overall health compared to a year ago (much better, somewhat better, about the same, somewhat better, much worse), and four items that yield a general health index (e.g., "I am as healthy as anyone I know.") Because two different response formats were used, raw scores were converted to z-scores. The internal consistency of the six items, estimated using Cronbach's alpha, was found to be 0.64, which was judged to be too low. When one question—"Compared to 1 year ago, how you would rate your health in general now?"—was dropped, alpha rose to 0.77. Therefore, the mean of the five z-scored items was used to operationally define SRH.

Competency in Everyday Functioning

The Patient Competency Rating Scale (PCRS) (91) elicits patients' self-rated competency in 30 specific activities that TBI commonly impairs (91). Thus, the PCRS was developed specifically for TBI and has been used with military TBI populations (92). The 30 items encompass four domains: cognitive, physical, emotional, and interpersonal, although in some study samples, a single factor loads both emotional and interpersonal items, creating a 3-factor structure (76, 85). The stem question is worded, "How much of a problem have you had (in the past month) in..."? Participants respond using a 5-point Likert Scale (1 = cannot do; 2 = very difficult to do; 3 = can do with some difficulty; 4 = fairly easy to do; 5 = can do with ease). The PCRS has demonstrated good internal consistency and predictive validity for return to work, community integration, and global functioning 1-year post-injury. Cronbach's alpha for the present sample was 0.92 for the overall scale, 0.81 for physical functioning, 0.84 for cognitive functioning, and 0.87 for emotional/interpersonal functioning. In the present analysis, the emotional functioning items were not used as they would be confounded with depressive symptoms.

Physical functioning was thus operationalized in two ways, using the Medical Outcomes Short Form Health Survey for veterans (SF-36V) and the Patient Competency Rating Scale (PCRS). Both are well-established measures of self-rated everyday functioning with different foci: the PCRS was designed specifically for TBI deficits, whereas the SF-36V was designed to capture everyday functioning in the general population. Importantly, both have a physical functional limitations component. **Table 1** presents the physical functioning items in the two scales. The overlap between these subscales dictated an analytical strategy using two regression models, described below.

Depressive Symptomatology

Depressive symptomatology was assessed with the 10-item Center for Epidemiologic Studies Depression Scale—(CES-D) short form (93). This screening instrument assessed the frequency of each symptom in the past week on a 0 (never or rarely) to 3 (every day) Likert scale, producing a possible range of 0–30, with higher scores reflecting higher depressive symptomatology. A cut-off score of 10 or higher indicates the presence of clinically significant depressive symptoms. The CES-D short form has well-established psychometric properties. In a large national sample of Operation Enduring Freedom (OEF, i.e., Afghanistan war) and Operation Iraqi Freedom (OIF, i.e., Iraq war) veterans (93), internal consistency of the CES-short from was reported as 0.91. Cronbach's alpha for the present sample was 0.85.

Procedure

The Institutional Review Board of the Corporal Michael J. Crescenz Veterans Affairs Medical Center VA Medical Center approved the study. Participants were interviewed in their homes by a trained interviewer. This interview provided information about participants' sociodemographic characteristics (including employment status), depression, and everyday functioning, as well as other background measures germane to the study (e.g., community reintegration). Comorbidities, TBI severity, and time post injury were obtained through a review of CPRS.

TABLE 1 | Two physical functioning measures: the Medical Outcomes Survey Short Form 36 vs. the Patient Competency Rating Scale (PCRS).

	Medical Outcomes Survey—Short Form—Veterans (SF-36) physical functioning scales	Patient Competency Rating Scale (PCRS)
Stem question	How limited are you in…?	How much of a problem have you had (in the past month) in… ?
Response format	A lot, a little, not at all	Cannot do, Very difficult, Somewhat difficult, Fairly easy, Can do with ease
ITEMS		
1.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	Preparing your own meals
2.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Dressing yourself
3.	Lifting or carrying groceries	Taking care of your personal hygiene
4.	Climbing several flights of stairs	Washing the dishes
5.	Climbing one flight of stairs	Doing the laundry
6.	Bending, kneeling, or stooping	
7.	Walking more than a mile	
8.	Walking several hundred yards	
9.	Walking one hundred yards	
10.	Bathing or dressing yourself	

Data Analyses

Bivariate relationships between each predictor and employment status were tested using independent measures *t*-tests or Chi-square tests, as appropriate. The potential predictors were years since most recent TBI, severity of most recent TBI, comorbidities (PTSD and pain), the SF-36V physical functioning subscale, and three PCRS domains (physical, cognitive, and interpersonal functioning), and depressive symptoms. The variables that revealed significant bivariate associations with employment status ($p < 0.05$) were selected as predictors in the subsequent analyses.

Hierarchical binary logistic multiple regression was used to test mediation. Although newer and more robust approaches such as structural equation modeling (SEM) to test mediation exist, (39, 94) hierarchical multiple regression was appropriate given the present study's smaller sample size (94–96). The data satisfied Baron and Kenny's (39) criteria to establish mediation (i.e., significant bivariate intercorrelations among independent, dependent, and mediating variables) (see below). Because employment status was a two-level dependent variable, binary logistic regression was used. The general analytic plan was to enter predictors in order of their modifiability from least to most, with background injury-related characteristics (e.g., time post injury) first, comorbidities next (PTSD, pain), and finally TBI sequelae, with physical health, functioning, and SRH in one block, and emotional sequelae (depressive symptoms) in the final block. Depressive symptoms were entered separately and after physical health/functioning because past research has cited depression as a mediator of other health conditions.

It is important to note that, for some study participants, higher education, rather than employment, may have been more important than employment. The GI Bill of Rights, a U.S. military benefit since 1944, provides financial support for college, graduate school, and training programs for veterans (97), and many veterans take advantage of this education benefit. In our study, 17 participants identified themselves as full-time students. To allow for the possibility that education may have been these veterans' primary goals (rather than employment), we conducted the regression analyses both with and without their data. SPSS version 20 was used for all analyses.

RESULTS

Description of Sample

Only about one-third of the veterans were employed, as shown in **Table 1**. None were voluntarily retired. Their mean age was 42 years, ranging from 23 to 67 years. Most (92%) were male. About 58% were white, 35% were Black, and 14% reported themselves as Hispanic or Latino. More than two-thirds were married, and 76% had children. **Table 2** also presents data on veterans' war cohort, source of TBI, number of TBI-incidents, TBI severity, comorbidities (e.g., PTSD), time since most recent TBI, and prevalence of major TBI-related sequelae. Most participants were veterans from Operation Iraqi Freedom (OIF), followed by those from Operation Enduring Freedom (OEF, i.e., the Afghan war). Time since the most recent TBI (time post injury) ranged from 1 to 45 years (for a Vietnam War veteran), with a mean of nearly 10 years. Almost one-third had experienced both blast and mechanical injuries. Thirty-six percent had experienced more than four TBIs, whereas only one-third reported a single TBI incident. Approximately 65% had a PTSD diagnosis, and 60% had a depression diagnosis documented in CPRS. **Table 2** presents these sample characteristics.

Bivariate Associations With Employment Status

Tests of zero-order associations of sociodemographic characteristics and comorbidities with employment status

TABLE 2 | Sociodemographic, medical, and military characteristics of the sample ($n = 83$).

	Percent (*n*)	Mean (*SD*)/range
Age		40.13 (13.20)/23–67 years
Gender (% male)	91.9 (76)	
EDUCATION		
Less than high school degree	6.0 (5)	
High school degree or GED	24.1(20)	
Some college	45.8 (38)	
College degree	16.9 (14)	
Postdoctoral degree	7.2 (6)	
Marital status (% married)	69.9 (58)	
Financial difficulty*		1.62 (1.09)/0–3
Employed	34.9 (29)	
RACE		
White	57.8 (48)	
Black	34.9 (29)	
Native Amer.	2.4 (2)	
Asian	1.2 (1)	
No primary/other	3.6 (3)	
Hispanic/Latino	14.0 (12)	
SEVERITY		
Mild	68.7 (57)	
Moderate-severe	31.1(26)	
WAR COHORT[3]		
OIF (Iraq)	61.4 (51)	
OEF (Afghanistan)	22.9 (19)	
Both OIF and OEF	10.5 (9)	
Prior to OEF/OIF	28.8 (24)	
Years since most recent TBI		9.99(11.09)/1.0–45.4 years
PTSD diagnosis	65.1 (54)	
Depression diagnosis	50.6 (42)	

**Difficulty paying for the basics such as housing, rated on a scale from 0 (not at all difficult) to 3 (extremely difficult).*

[3] Does not sum to 100% because some veterans served in multiple war cohorts.

revealed no associations. Employment status was found to be significantly associated with the pain index of the SF-36V; physical functioning as measured by both the PCRS and the SF-36V; the SRH index; the cognitive functioning factor of the PCRS; and depressive symptoms. Therefore, only these variables were used in the logistic regression analyses. **Table 3** presents these bivariate findings.

Bivariate Associations Among the Predictors

An assumption of multiple regression mediation analyses is that independent variables and mediators must be correlated with the dependent variable and with each other. In these data, the requirement was met. CES-D scores were found to be correlated with both SF-36V physical functioning ($r = 0.42$, $p < 0.0001$) and the PCRS physical functioning measure (mean $= -0.56$, $p < 0.0001$). The pain index was also strongly associated with both SF-36V ($r = 0.61$, $p < 0.0001$) and the PCRS measures of physical functioning ($r = -0.49$, $p < 0.0001$). All had bivariate associations with employment status (**Table 2**).

Logistic Regressions

The pain index (a comorbidity) was entered on block 1; physical functioning, cognitive functioning, and SRH on block 2; and depressive symptoms on block 3. Because physical functioning was operationally defined in two ways, using the SF-36V and the PCRS physical functioning measures, a separate regression was conducted for each physical functioning measure.

Regression Using SF-36V Measure of Physical Functioning

On block 1, the pain index revealed an association with employment status, but this association became nonsignificant when the physical health/functioning variables were entered on block 2. Among those block 2 predictors, only physical functioning demonstrated an independent association with employment status. On block 3, the entry of depressive symptoms significantly attenuated the physical functioning effect, leaving depressive symptoms as the sole significant predictor. **Table 4** presents these findings. **Figure 1** displays the mediation effects.

Regression Using the PCRS Measure of Physical Functioning

As with the previous regression model, pain (block 1) lost its predictive ability when physical health/functioning variables were entered on block 2, but none of these individual predictors independently predicted employment. Thus, the PCRS measure of physical functioning did not predict employment status, as the SF-36V definition had. Only depressive symptoms, entered on block 3, demonstrated a significant independent contribution to employment status. **Table 5** presents these regression findings.

Regression analyses, performed without the 17 cases of full-time students, produced results not substantially different from the analyses using the full sample.

DISCUSSION

Pain was a significant predictor of employment status, but its effect was attenuated by the physical health and functioning variables—among which physical functioning, as measured by the SF-36V, was the sole significant predictor in block 2. This physical functioning effect in turn was attenuated when depressive symptom scores were entered into the regression model. Mediation was total. These findings illustrate the value of mediation analyses in yielding insights into the contributions of predictors of TBI outcomes, in this case employment status. Mediation analyses have particular utility for tertiary prevention of poor TBI outcomes, an important aim in light of the many TBI patients left with chronic TBI symptoms after post-acute rehabilitation ends.

For the PCRS measure of physical functioning, this effect was not demonstrated. Neither the PCRS measures of cognitive or physical functioning, although both had bivariate association, made independent contributions to employment status. By contrast, it is interesting to note the utility of the SF-36V

TABLE 3 | Bivariate associations between employment status and predictor variables: results of *t*-tests or Chi-square tests.

Predictor	Employed mean (SD) or % (n)	Unemployed mean (SD) or % (n)	t (df)	Chi^2 (df)/ Fisher's exact	*p*
Age	37.03 (12.67)	41.72 (13.03)	1.578 (81)		0.118
Sex [male (72)]	34.2 (26)	65.8 (50)		.	0.691
Race [White (46)]	33.3 (16)	66.7 (32)		0.129 (1)	0.719
Hispanic ethnicity (11)	36.4 (4)	63.6 (7)		0.011 (1)	0.915
Financial difficulty	1.45 (0.10)	1.69 (1.11)	0.961 (81)		0.339
Marital status (married(56)]	36.2 (21)	63.8 (37)		0.061 (1)	0.804
Education [> high school (56)]	39.7 (23)	60.3 (35)		1.917 (1)	0.166
PTSD [diagnosis present (51)]	29.6 (16)	70.4 (38)		1.884 (1)	0.170
Pain [Diagnosis present (53)]	32.1 (18)	67.9 (38)		0.916 (1)	0.339
Tinnitus [Diagnosis present (21)]	47.6 (10)	52.4 (11)		1.853(1)	0.173
Photosensitivity [Diagnosis present (17)]	23.5 (4)	76.5 (13)		1.344 (1)	0.246
Years since TBI	7.43 (9.22)	11.36 (11.82)	1.56 (81)		0.124
TBI severity [mTBI (56)]	40.4 (23)	59.6 (20)		2.344 (1)	0.126
Depressive Symptoms (CES-D)	15.00 (6.30)	20.17 (5.50)	3.88 (81)		< 0.001
SF-36V (PHYSICAL HEALTH/FUNCTIONING COMPONENTS)					
Physical functioning	5.28 (4.61)	9.65 (4.72)	4.06 (81)		0001
Pain severity	2.79 (1.05)	3.43 (1.25)	2.32 (81)		0.023
Extent pain interferes with work*	1.93 (1.36)	2.65 (1.20)	2.48 (81)		0.015
Pain Composite	2.36 (1.13)	3.04 (1.14)	2.57 (81)		0.012
SELF-RATED FUNCTIONING (PCRS)**					
Cognitive	3.00 (0.76)	2.71 (0.54)	2.00 (81)		0.049
Interpersonal	3.32 (0.82)	3.09 (0.70)	1.37 (81)		0.174
Physical	4.24 (0.45)	3.12 (81)	3.12 (81)		0.002

**Mean of pain severity and pain interference scores.*

***Patient Competency Rating Scale, omitting emotion items to avoid confounding with depressive symptoms.*

TABLE 4 | Binary logistic regression results: employment status' association with predictors (using SF-36V definition of physical functioning), demonstrating mediation of pain effects by physical health/functioning and mediation of physical functioning by depressive symptoms (Nagelkerke $R^2 = 0.313$, $p = 0.001$).

	B (Std error)	Wald (df)	*p*	Exp(B)	95% CI	
					Lower	Upper
BLOCK 1						
Pain (severity and interference with normal work)	−0.508 (0.211)	5.820 (1)	0.016	0.602	0.399	0.903
BLOCK 2						
Pain (severity and interference with normal work)	−0.078 (0.287)	0.073 (1)	0.787	0.897	0.517	1.556
Self-rated health	−0.071 (0.489)	0.021 (1)	0.885	0.752	0.248	2.278
Cognitive functioning (PCRS)	0.261 (0.431)	0.368 (1)	0.544	1.322	0.569	3.073
Physical functioning (SF-36V)	−0.176 (0.075)	5.578 (1)	0.018	0.833	0.721	0.962
BLOCK 3						
Pain (severity and interference with normal work)	−0.038 (0.291)	0.017 (1)	0.897	0.923	0.526	1.619
Self-rated health	0.097 (0.510)	0.036 (1)	0.850	0.879	0.282	2.743
Cognitive functioning (PCRS)	−0.451 (0.548)	0.679(1)	0.410	0.669	0.230	1.740
Physical functioning (SF-36V)	−0.148 (0.076)	3.821 (1)	0.051	0.854	0.738	0.989
Depressive symptoms	−0.133 (0.057)	5.445 (1)	0.020	0.878	0.786	0.981

measures of health and functioning, especially bearing in mind that this tool was not originally intended for a TBI population. Inspection of the two measures (**Table 1**) suggests that the items in the PCRS measure closely correspond to instrumental activities of daily living (i.e., self-care activities), whereas the SF-36V items address a broader range of basic physical activities including walking, bending, lifting, and climbing stairs. The SF-36V measure also included more items overall. In addition to

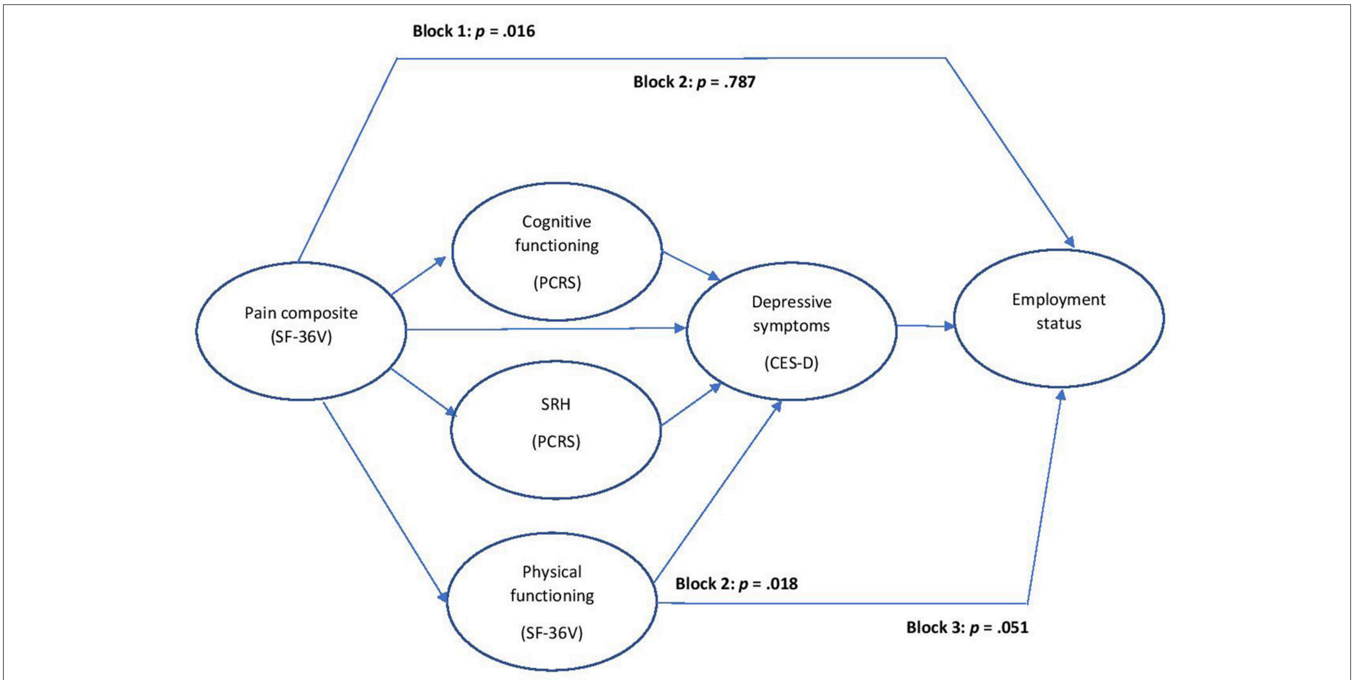

FIGURE 1 | Mediation effects: pain effect mediated by physical/health functioning (at Block 2); physical functioning effect mediated by depressed symptoms (at Block 3).

TABLE 5 | Binary logistic regression results: employment status association with predictors (using PCRS measure of physical functioning), demonstrating mediation of pain effect by physical health/functioning (Nagelkerke $R^2 = 0.259$, $p = 0.001$).

	B (Std error)	Wald (df)	*p*	Exp(B)	95% CI Lower	95% CI Upper
BLOCK 1						
Pain (severity and interference with normal work)	−0.508 (0.211)	5.820 (1)	0.016	0.602	0.398	0.905
BLOCK 2						
Pain (severity and interference with normal work)	0.178 (0.265)	0.450 (1)	0.503	0.779	0.471	1.287
Self-rated health	0.326 (0.437)	0.557 (1)	0.455	1.126	0.412	3.076
Cognitive functioning (PCRS)	0.199 (0.460)	0.187(1)	0.665	1.265	0.517	3.095
Physical functioning (PCRS)	0.822 (0.513)	2.569 (1)	0.109	2.263	0.838	6.113
BLOCK 3						
Pain (severity and interference with normal work)	−0.176 (0.283)	0.389 (1)	0.533	0.767	0.446	1.321
Self-rated health	0.411 (0.465)	0.780 (1)	0.377	1.184	0.409	3.426
Cognitive functioning (PCRS)	−0.438 (0.554)	0.626 (1)	0.429	0.693	0.239	2.010
Physical functioning (PCRS)	0.475 (0.569)	0.695 (1)	0.405	1.598	0.531	4.806
Depressive symptoms	−0.137 (0.058)	5.497 (1)	0.019	0.875	0.781	0.980

its measure of physical functioning, SF-36V measures of pain and SRH were associated with employment status. These results highlight the value of the SF-36V for TBI research.

Considering that most of the sample had an mTBI, the finding that limitations in physical functioning predicted employment status was somewhat surprising. Yet, many previous TBI studies have identified physical functioning limitations as a predictor of employment status. The fact that this variable as measured by the SF-36V and the CPRS showed significant bivariate associations with employment argues against measurement error as an explanation. Nevertheless, the possibility exists that non-TBI injuries in this population, drawn from a polytrauma population, may have accounted for the physical functioning findings. A replication of this effect using a civilian sample with less polytrauma should address this interesting question.

Although employment may be thought of as a component of CR and even as a possible proxy for it, it should be noted that in the present data set, CR and employment status were not strongly associated ($r = 0.21$, $p = 0.054$). Therefore, the findings of mediation of physical functioning effects on employment outcomes by depressive symptoms contributes evidence for the robustness of depression's effect.

In the present sample of military veterans with TBI, no sociodemographic characteristics were associated with employment status. This differs from findings of many studies of civilian TBI. It is possible that, because of participants' shared backgrounds in the military, some sociodemographic characteristics (i.e., previous employment, sex, number of years of education) varied less than would be the case in civilian TBI samples. Similarly, TBI severity was not associated with employment status, possibly reflecting the predominantly mild or moderate severity status of this sample.

Cognitive functioning, defined using the PCRS cognitive domain, was also not found to be a predictor of employment status. This may reflect the fact that this variable was a self-rated measure, rather than based on neuropsychological test scores, which some studies have found to be predictive of employment outcomes (12, 24). The fact that the present sample included few patients with severe TBI could also help account for the absence of effects for cognitive functioning.

Findings underscore the central role of depression in the employment status of veterans with TBI. They echo earlier research (58) that showed depressive symptoms mediated effects of both physical functioning and PTSD diagnosis on community reintegration in veterans with TBI.

Study Limitations

Although hierarchical multiple regression was appropriate given the study's relatively small sample size, SEM or other methods might be more powerful for testing mediation in larger samples (98). The mediating role of depression in employment status has not been identified in previous TBI research, and thus it warrants further examination in future studies having larger and more diverse samples. A larger sample might demonstrate statistically significant effects for the mediated predictors, revealing partial mediation for some of the predictors. Our findings should be considered preliminary until they can be replicated in such samples using different mediation methods.

Because multiple regression analyses are correlational, inferences about the direction of causality should not be drawn. For example, unemployment may itself be a cause of depression, rather than an effect of it. Furthermore, depression may have existed prior to the TBI, rather than being an effect, and may have contributed to functional limitations. The present investigation did not have access to information about time of onset for depression. These possibilities complicate interpretation of the findings. Thus, an interesting issue for future research might be whether time of onset of depression makes a difference in findings. In addition, the study's cross-sectional design precludes interpretation of temporal relationships, which might be addressed with longitudinal data. Most of our sample had experienced mild TBI with persistent post-concussive symptoms, and 12% had mild to moderate TBI. This preponderance of milder TBI cases may help account for differences from earlier studies with patients with primarily moderate to severe TBI reporting severity as a predictor of work outcomes (22, 23).

The generalizability of study findings may be limited because this sample consisted of veterans enrolled in outpatient services at a VA rehabilitation service. Future research should include samples of civilians with TBI, as well as veterans with TBI who are *not* using VA services. In our sample, 89% had clinically significant levels of depressive symptoms, which is likely to be higher than in civilian TBI populations. Nevertheless, TBI populations do have a high prevalence of depressive symptoms and depression diagnoses (99).

Questions remains about other mediators and specifically whether variables entered earlier in the model (e.g., pain, here treated as a comorbidity and therefore entered on block 1) may themselves mediate effects of variables entered later. Such questions would rely on theoretical rationales regarding causality and may be interesting directions for further research.

Other Directions for Future Research

Moderation analyses should also be more routinely employed in research on employment and TBI. Whereas mediation speaks to how or why relationships occur, moderation reflects the direction and/or strength of the relation between an independent and a dependent variable (39). Usually represented as interactions, moderators may shed light on ways in which predictors interact to produce effects. Given the size and richness of research on employment status and TBI, researchers should employ more moderation approaches.

Some participants were in school, utilizing their GI Bill education benefits, rather than employed. This was addressed by conducting the analyses without data from those in school fulltime and not working. The fact that education, rather than employment, may be a primary rehabilitation goal may be an issue for civilian samples as well, given that many young school-age adults sustain TBI. Research with large civilian TBI samples could examine whether college/training attendance have similar predictors as employment status.

Clinical and Research Implications

TBI rehabilitation often aims to return persons with TBI to meaningful employment, which helps them restore previous social roles, promotes socialization, improves psychological well-being, and increases opportunities for building relationships. All of these are part of reintegrating into the community, the premier goal of rehabilitation (100). The ability to work also has implications for the family and its financial status. Financial difficulty has been shown to predict depressive symptoms in family caregivers of veterans with TBI (101). The patient's inability to work thus may also have effects on caregiver well-being.

Study findings underscore the value of mediational analyses in shedding light on how risk factors "work together" to affect outcomes of interest (102). They argue that mediational analyses should be used more routinely in research on important TBI outcomes such as employment. Because depression is amenable to treatment, its recognition as a mediator provides opportunities to influence important health outcomes, particularly as a means of tertiary prevention. The present findings suggest that the negative effects of pain and/or physical functioning limitations on employment could be mitigated by more effective treatment of depression. Therefore, routine assessment of depressive symptoms and aggressive treatment of depression should promote the success of rehabilitation in improving employment outcomes for individuals with TBI.

ETHICS STATEMENT

The Institutional Review Board of the Corporal Michael J. Crescenz Veterans Affairs Medical Center in Philadelphia, PA approved the study and the study protocol. Informed consent was obtained using a Veterans Affairs written consent form for human participants. This study was carried out in accordance with the requirements of the Institutional Review Board of the Corporal Michael J. Crescenz Veterans Affairs Medical Center with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Lawsuit and Traumatic Brain Injury: The Relationship Between Long-Lasting Sequelae and Financial Compensation in Litigants. Results From the PariS-TBI Study

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Purpose: People with traumatic brain injury are frequently involved in a litigation because another person was at fault for causing the accident. A compensation amount will often be settled to compensate the victim for the past, present, future damages and losses suffered. We report descriptive data about the full and final personal compensation amount and investigated its association with patient's outcomes.

Methods: We used a longitudinal prospective study of severe TBI patients injured in 2005–2007 (PariS-TBI). Questions regarding involvement in a litigation were asked concurrently with 4 and 8-year outcomes.

Results: Among 160 participants assessed 4 and/or 8 years post-injury, a total of 67 persons declared being involved in a litigation, among which 38 people reported a compensation amount of a mean €292,653 (standard deviation = 436,334; interquartile 25–50–75 = 37,000–100,000–500,000; minimum = 1,500-maximum = 2,000,000). A higher compensation amount was associated with more severe disability and cognitive impairment in patients, and with more informal care time provided by caregivers. However, no significant association related to patient's gender, age, years of education, motor/balance impairment, return to work status, mood and related to caregiver's subjective burden was found.

Conclusion: Financial compensation was related to victims' long-term severity of impairment, although some extreme cases with severe disability were granted very poor compensation.

Keywords: traumatic brain injury, litigation, compensation, disability, Paris-TBI, follow-up, lawsuit

INTRODUCTION

Traumatic brain injury (TBI) occurs at a high incidence with more than 50 million people sustaining a TBI each year worldwide (1). Related to this, people with TBI are frequently involved in a litigation with claim compensation proceedings because another person was partly or wholly at fault for causing the injury, in particular in the context of road traffic accidents. While lawsuits after TBI are frequent, research exploring how litigation and long-term TBI outcomes relate to each other is, on the contrary, quite rare (2).

Litigants who sustained a TBI might hire a private attorney or conduct direct negotiation and settlements with insurance companies that both often recourse to some clinical expertise. Together, they will document the personal injury case in order that a monetary value is settled for the past, present and future damages and losses suffered. The health state and the social economic position in which the victim would have been if the accident had not occurred are considered to determine the personal compensation amount (and life rents when applicable) (3). Yet, settling such a monetary value entails numerous levels of complexities and final compensation amounts settled by the court or during out-of-court negotiations vary widely, at least within the French medico-legal context.

There is a lack of knowledge in the literature about personal compensation amounts after TBI, and reports exploring their relationship with TBI long-term outcomes and needs of patients and families are rare. The litigation process in France is entirely separated from clinical care with distinct physicians for both, and information about litigation usually comes from family associations. People sustaining a TBI are not all adequately and equally informed about litigation procedures in France, and some of them do not seek support or advice from a lawyer. Litigation is also a challenging process because cognitive-behavioral impairment requires complex and in-depth evaluations to assess TBI full and long-term impact. As opposed to physical, orthopedic, and motor deficiencies that have often straightforward consequences, the relation of cognitive-behavioral impairment to the disability situation of the victim (in terms of functional outcome in daily life) remains varied and complex to assess.

TBI causes major long-lasting neurological impairments and the related disability is associated with a huge burden for patients and families (1). While litigation process is often a long and stressful experience for TBI litigants (4), it also brings financial compensation that might positively modulate the future life and quality of life of patients and families (5). Thus, investigating whether personal compensation amount is related to the level of disability and needs of the victim seems crucial. We sought here to report descriptive data about the full and final personal compensation amount and long-term patient's outcomes for people with severe TBI who sustained an accident caused by another party. We took the patient's perspective and only investigated the capital sum awarded to the patient by the defendant insurance (i.e., not including the social and medical health expenses paid by the defendant insurance to the health care system, and not including the potential annuities that might be additionally paid by the employer to the patient in case of a work-related injury). We used research follow-up data from the PariS-TBI study (i.e., a French longitudinal inception cohort study of patients with severe TBI, as opposed to a medico-legal dataset). In a previous work using the PariS-TBI study data (4), we showed that those patients involved in a litigation procedure within French jurisdiction compensation scheme had a worse prognosis 4 years after the accident than non-litigant patients in terms of autonomy, participation and psychiatric function. The present extension study on litigation data in PariS-TBI study aims to further investigate the relationship between final personal compensation amount and patient's outcomes after the court verdict or end of negotiations.

METHODS

This study is part of the larger PariS-TBI study undertaken in 2005 in the Parisian area. PariS-TBI is an ongoing inception population-based cohort of individuals with a severe TBI, for which prospective collection included pre-traumatic and early data, and follow-up assessments 1, 4, and 8 years post-injury. Individuals aged 15 or more who had sustained a severe TBI (initial Glasgow Coma Scale score ≤ 8) were consecutively recruited by mobile emergency services over a 22-months period, and assessed in acute care. A total of 504 patients were included (76% men, mean age 42 years). Causes of injury were road traffic accident for 266 (53%), accidental falls for 116 (23%), non-accidental falls for 67 (13%), aggression for 25 (5%), and unknown for 30 (6%). Acute care mortality was 49%, and 134 followed by 147 and 86 survivors were followed-up at 1, 4, and 8 years post-injury, respectively. The 4- and 8-years assessment covered a broad range of impairments, activities, and participation, including questions about the litigation procedure in the form of a face-to-face interview carried out by a neuropsychologist in participant's home. No financial compensation was given to volunteering patients and caregivers. The detailed methodology, longitudinal results and potential biases related to lost-to-follow-up patients have been previously reported (6–13).

Socio-demographic data (age, gender, years of education) and initial severity data [Glasgow Coma Scale score and Injury Severity Score (ISS) (14)] were included. The ISS is an anatomical scoring system that screen for multiple injuries divided into six body regions (head, face, chest, abdomen, extremities including pelvis, and external). In each of these body regions, the severity of the respective injury is assessed on a six-point ordinal scale called the Abbreviated Injury Scale (AIS) and the total ISS score is obtained from the three most severely injured regions that are squared and summed. Patient's assessments at 4 and 8 years included: the Glasgow Outcome Scale-Extended (GOS-E) (15), which covers seven main areas (consciousness, independence at home, independence outside the home, work, social and leisure activities, family and friends, return to normal life) and provides an ordinal classification of disability in eight categories, ranging from death to upper good recovery; the working status (return to work); the Barthel Index which assesses functional independence and mobility in activities of daily living (16); the motor and balance impairment was assessed through a dichotomized score (motor and/or balance disorders, or not); the DysEXecutive questionnaire (DEX) (17) which measures occurrence of cognitive, behavioral, and emotional changes as a result of impairment of executive functions completed by the primary caregiver of the patient; the Hospital Anxiety and Depression scale (HAD) (18). Caregiver's assessments at 4 and 8 years included: the average informal care time provided to the patient per day (i.e., time dedicated to basic and instrumental activities of daily life and supervision) assessed thanks to the Resource Utilization in Dementia battery (RUD) (19); the measure of level of perceived burden thanks to the Zarit Burden Inventory (ZBI) which enable grading the severity of burden experienced by the caregiver into four groups (mild, mild to moderate, moderate to severe, and severe burden) (20). In addition, patients and their relatives were asked whether they were involved in a litigation procedure (i.e., victim of an injury caused by another responsible party and involved in a lawsuit compensation claim related to this injury). When the litigation procedure was settled, patients were asked to report the full and final compensation amount (rounded, in euros) offered and agreed with the opposing party.

Statistical analyses were performed using STATA v14 and R 2.12.0. Comparisons between groups (men vs. women; those people who returned to work vs. those who did not; those with motor and/or balance impairment vs. those without this impairment) were performed using Wilcoxon or Mann–Whitney tests. Spearman correlation tests were used to evaluate the association between the compensation amount and patients' and caregivers' sociodemographic and clinical data.

In accordance with French legislation, patients and their relatives were informed about the inclusion in the database and informed written consent was obtained before each assessment. Approval from Commissions that enforce research database legislation in France and approval from the Ethical Committee (Comité de Protection des Personnes XI) was obtained before each assessment. The study was registered in ClinicalTrials.gov in August 2011 (identifier: NCT01437683).

RESULTS

Among 160 participants assessed 4 and/or 8 years post-injury, 67 persons declared being involved in a litigation. The litigation was over after 4 and 8 years for 25 and 32 people, respectively, while still in progress for 10 of them, and a total of 38 people (65%) agreed to report the final compensation amount awarded (**Figure 1**). These 38 litigants included 29 men and 9 women, and the cause of the TBI was road traffic accident in 31 cases, physical aggression in 2 cases and unknown in 5 cases. Regarding litigants with a report of a compensation amount ($n = 38$) vs. those litigants without a report of a compensation amount ($n = 29$), there was no significant differences in socio-demographic and clinical scores (all $p > 0.05$), except for the Zarit Burden Inventory which was lower in litigants with a report of compensation amount (ZBI = 22.9 vs. ZBI = 33.3; $p = 0.04$). Among them, 34 were aged below 70 years of age, including 23 people who were not working and 11 who had a professional activity. Patients' and caregivers' characteristics and scores are presented in **Table 1**.

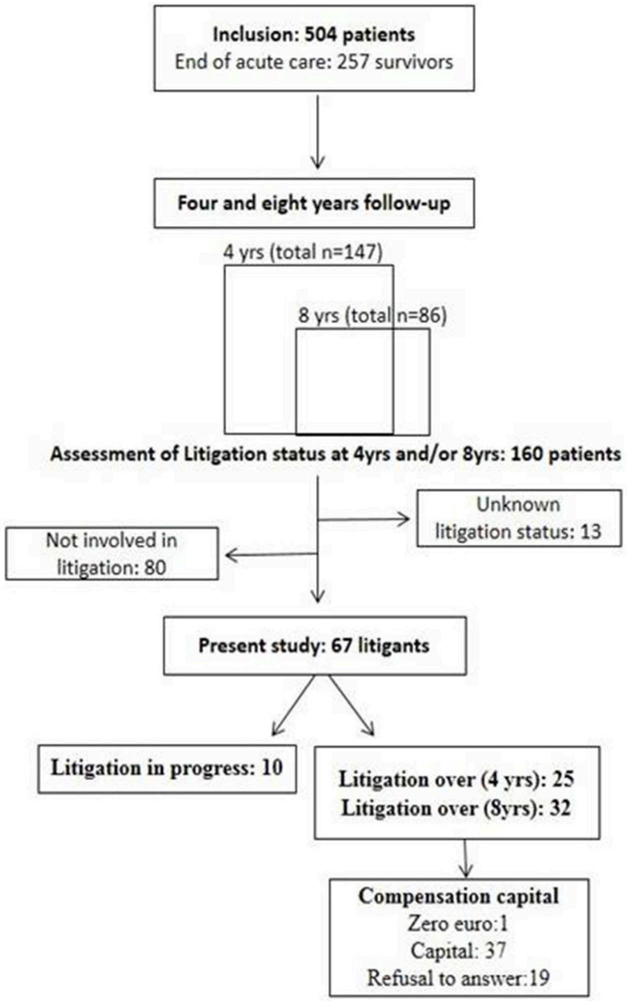

FIGURE 1 | Flow chart depicting PariS-TBI cohort and the litigation study.

The final settlement amount was zero euro for 1 person and a mean €292,653 (standard deviation = 436,334; interquartile 25–50–75% = 37,000–100,000–500,000; minimum = 1,500–maximum = 2,000,000) for the others. Among the most severe patients (with GOS-E scores 3 and 4), 4 patients had a low amount below 88,000 euros. There was a non-significant tendency ($p = 0.2$) for higher compensation amount in men with a mean €343,166 (standard deviation = 490,184; median = 100,000; minimum–maximum = 5,000–2,000,000) as opposed to a mean €135,500 (standard deviation = 95,298; median = 115,000; minimum = 1,500–maximum = 300,000) in women. In those people below age 70 eight years post-injury ($n = 34$), there was a non-significant tendency ($p = 0.08$) for higher compensation amount awarded in those who had not returned to work ($n = 23$) with a mean

TABLE 1 | Demographic characteristics and TBI outcomes.

Variables	Mean (standard deviation; minimum – maximum) or count (%)
DEMOGRAPHIC CHARACTERISTICS	
Age (eight years post-injury)	37.5 (15.3; 20.3–80.3)
Years of education	12.7 (3.3; 9–22)
INJURY SEVERITY	
Initial Glasgow Coma Scale (min–max = 3–15)	5.6 (1.8; 3–8)
Injury Severity Score (min–max = 0–75)	31.9 (9.9; 14–50)
PATIENTS AND CAREGIVER FOLLOW-UP OUTCOMES	
Glasgow Outcome Scale-Extended (1 = death to 8 = upper good recovery)	5.4 (1.3; 3–8)
DysEXecutive questionnaire (min-max = 0–80)	24.9 (15.1; 0–71)
Motor and/or balance deficiency (yes)	15/38 (39%)
Hamilton Anxiety and Depression scale (min-max = 0–42)	12.6 (8.5; 0–29)
Barthel index (min-max = 0–100)	97.4 (7.2; 70–100)
Ressource Utilization in Dementia scale (min-max = 0–24)	6.5 (8.5; 0–24)
Zarit Burden Inventory (min-max = 0–88)	22.9 (16.2; 0–59)

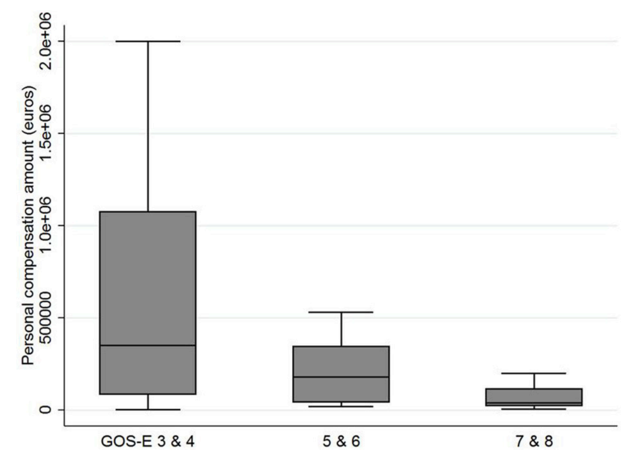

FIGURE 2 | Final personal compensation amount offered to litigants as a function of the Glasgow Outcome Score-Extended. Disability level, number of patients (*n*) and age (mean, range[]) per category: GOS-E 3 and 4 = severe (*n* = 10; 43.6 [22-80]); 5 and 6 = moderate (*n* = 16; 39.2 [21-71]); 7 and 8 = light (*n* = 11; 29.7 [20-48]).

€407,094 (median = 2,00,000; standard deviation = 516,331; minimum = 1,500–maximum = 2,000,000) vs. a mean €117.727 (median = 80,000; standard deviation = 134,498; minimum = 5,000–maximum = 420,000) in those who had returned to work ($n = 11$). There was no difference in compensation amount ($p = 0.9$) in those with motor and/or balance impairment with a mean €293,333 (standard deviation = 415,464; minimum–maximum = 63,257–523,409) as opposed to mean €292,189 (standard deviation = 459,679; minimum–maximum=88,378–495,999) in those without such deficiency.

Regarding socio-demographic data, no correlation was found between compensation amount and age or years of education ($p = 0.9$ and $p = 0.3$, respectively). Regarding initial severity, no correlation was found between compensation amount and Glasgow Coma Score or ISS ($p = 0.4$ and $p = 0.7$, respectively). Regarding patients' 4 and 8 years outcomes (depending on when the verdict happened): a higher compensation amount was associated with a more severe disability as assessed with the GOS-E (Spearman's rho = 0.4, $p = 0.01$ as illustrated on **Figure 2**); a higher compensation amount was associated with more severe cognitive impairment on the DEX (Spearman's rho = 0.4, $p = 0.02$); no such association was found with the Barthel index score ($p = 0.1$) nor for anxiety and mood (HAD, $p = 0.2$); in caregivers, a higher compensation amount was associated with more informal care time devoted to the patient (rho = 0.66, $p = 0.01$) but not with a higher subjective burden (ZBI) ($p = 0.07$).

DISCUSSION

TBI lawsuit settlements result in a secure financial capital in the form of a personal compensation amount offered to the victims who sustained an accident caused by another party. Personal compensation amount were variable, and a higher compensation was found associated with more severe levels of global handicap, of executive dysfunction and of informal care time, but no significant association was found with patients' age, years of education, initial severity scores (including the ISS which takes into account extracranial injuries), motor-balance impairment, return to work, mood nor with subjective burden in caregivers. These figures and associations are discussed in light with the possible mediating factors that were unmeasured given the exploratory nature of the present study.

In France, negotiations and medico-legal expertise around personal compensation use various abacuses to support objectivity in the medico-legal proceedings, assessing a systematic range of heads of damages (including pecuniary and non-pecuniary sectors, temporary and permanent damages, and damages to direct and indirect victims) (21). We report here the full and final personal compensation amounts granted to individuals (i.e., not including the social and medical health expenses paid by the defendant insurance to the health care system).We found a substantial variability in personal compensation amounts ranging from €1,500 to €2,000,000 (i.e., $1,709 to $2,278,982). Original research and reports on financial compensations in TBI victims are lacking in France and elsewhere, making explanations and comparisons in the field challenging. Jou's group is one of the few to use data about compensations that perpetrators were ordered to pay in court verdicts in 2013 in new Taiwan dollars (22, 23). Yet, the authors did not focus on verdict compensation amounts but rather used them to assess the amount that road accident perpetrators were willing to pay to compensate their victims. Using hypothetical scenarios (contingent valuation method) they found that perpetrators were willing to pay more consolation compensation with increased injury severity. Data about compensations amount in the community stem from law firms freely available on the web providing ranges of values or case results: for instance a range from £1,940 to £11,200 (i.e., \$2,452–14,154) in mild head injury and a range from £247,280 to £354,260 in major head injury (i.e., \$312,498–447,694) can be found in the United Kingdom (24); for instance an isolated case reported very high monetary values of \$17.4 million (granted to a 27 years old man injured by a truck in 2012) (25) or a set of case results reported a range from \$100,000 (mild concussion) to \$26 million (permanent brain damage) in the United States (26). Yet one must keep in mind that these data are displayed by the law firms to inform the general population and also for the firms marketing purposes, but not for scientific research.

That higher compensation amounts were positively correlated with more severe handicap (as assessed by the routine score GOS-E) seems reinsuring: it suggests that finances granted through litigation are adapted to the level of recovery and needs of victims who often experience a socio-economic precarity due to TBI (because of the loss of a job and a regular income for instance) (1). While we did not find research documenting such a congruent relation between global disability and financial settlement, this result aligns with legal information freely available in the community (27). As the prolonged process of litigation against a defending party might have a negative impact on patient's recovery and community reentry (2, 4, 28), it is necessary to show positive benefits in the form of financial award to confirm that victims should proactively pursue lawsuits. For instance, financial compensation was found to have a protective effect against late mortality following rehabilitation for severe TBI (through interactions with rehabilitation service variables), suggesting that wider access to compensation (and rehabilitation) might further improve life expectancy in TBI (5).

The correlation with cognitive disorders is interesting as cognitive impairment is a core factor impacting negatively patients' quality of life, autonomy, community reentry and economic status (1, 6, 7). While cognitive-behavioral sequelae might be sometimes overlooked as a consequence of unawareness of invisible impairment they were associated here with a higher compensation amount while motor-balance impairment was not. The correlation between compensation amount and caregiving needs (as assessed by the number of informal caregiving hours devoted to the patient) seems also an interesting finding as informal caregivers are often called "ricochetting victims" (4, 5). Informal caregivers are known to bare the burden of care in TBI and the economic valuation of their informal work in litigation represent a significant financial head of damage (1, 5).

Surprisingly though, the financial compensation did not significantly differed among those litigants who worked again vs. those who did not. This might appear counterintuitive as compensation is being capitalized on years lived with a disability and typically on loss of earnings and career chances related to the head of damages "return to work" (3, 21). It might be that our sample size was too small to ascertain this tendency statistically. Also, a younger age might not be associated with a higher amount maybe because capitalization of the career loss could not be achieved in patients who were students at the time of the accident. The non-significant relation between compensation amount and initial severity of the injury might point out a relative small impact of the initial damages as opposed to appraisal of long-term sequelae and social and economic heads of damages.

The findings of the present study should be interpreted with caution though as many parameters might play a role in the compensation process. Apart from the severity of the injury and of the associated impairments, a set of other unmeasured factors here might account for court outcomes and compensation amounts. For instance, pre-injury chronic conditions classically assessed in epidemiology with the Charlson comorbidity score were not measured here. Yet, premorbid impairments could contribute along with the consequences of the TBI to the global disability of people and to the various impairments and informal care needs measured here, while logically not resulting at the same time in a higher financial compensation. In that case, forensic evaluation should adequately disentangle medical and social economic consequences uniquely related to TBI from those related to prior conditions and comorbidity. We do not know the cause about poor compensation in some individuals of the sample and might only make assumptions based on care experience. Sometimes the expertise process might result in a rather unfair settlement (with extreme cases where people with most severe disability were granted very poor financial compensation amounts for life). In the case of an unfair compensation system, health professionals would be strongly encouraged to refer litigant patients to specialized attorneys or consulting physicians to assist them in this complex process. Yet, isolated TBI vs. TBI associated with multiple extra-cranial injuries might also account for a great inter-individual variability of compensation amounts. Other categories of loss that were not capture in the present study, such as esthetic impairment, loss of sexual function, loss of the prospect of founding a family, pain, expenses of accommodation, and vehicle conversion, loss of opportunity regarding education could result in ascertainment bias of our results. These unmeasured factors might account for the extreme cases we observe where people with most severe disability were granted very poor financial compensation amounts for life. In addition, other external factors such as the attorney's skills, and insurance expert's experience (or reversely, malpractice leading to underreporting of impairment), the court jurisdiction specificities, the solvability of the opposing party, the influence of personality of patients during legal proceedings might also negatively (or positively) influence the settlement of the final compensation outcome and account for these disparities in amounts and consequential social inequalities. A final issue is that a number of patients were lost to follow-up, as in most long-term follow-up research. As previously reported, included patients one and four-year post injury did not significantly differ from lost-to-follow up patients in terms of injury severity, However, social and demographic factors such as unemployment before the injury or pre-injury alcohol abuse were significantly associated with loss to follow-up (8). This may be a potential source of bias.

As a whole, caution is needed because of the small size of the sample and further research is warranted to continue investigating these compensation outcomes and associations in other international settings and larger datasets. Future study should examine in detail the full list of losses and outcomes related to predicted life path. Inclusion of financial life rents and all other types of medical expenses and reimbursements of acute and long-term care would also provide a better overview of the compensation situation. The main limitations of the present study lie in the small sample size that does not permit to compute multivariate model analyses, and in the limited list of heads of damage available here, including identifying from the start isolated TBI vs. TBI associated with multiple extra-cranial injuries. A strength however lies in the nature of PariS-TBI study that was not meant to gather clinicolegal data but rather provides a neutral independent setting of examination in the context of litigation.

AUTHOR CONTRIBUTIONS

EB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EB, CJ, AR, and PA: concept and design; All authors: acquisition, analysis, or interpretation of data; EB, CJ, AR, and PA: drafting of the manuscript; All authors: critical revision of the manuscript for important intellectual content; EB, IG, and CJ: statistical analysis; CJ: obtained funding; EB, CJ, PA, IG, PA, and LM: administrative, technical, or material support; PA: supervision.

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Hit in the Heart of Life: How Meeting Like-Minded Peers May Contribute to Psychosocial Recovery of Adolescents and Young Adults With Acquired Brain Injury

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Adolescents and young adults are often in a particularly vulnerable position following acquired brain injury (ABI). In addition to neurological and cognitive impairment, they are faced with issues concerning education, job, family, and social life. Moreover, they may be limited in meeting peers and may be left alone with psychosocial issues. This paper investigates how this patient group may benefit from meeting like-minded peers. From information gathered through a questionnaire and interviews with participants in a peer support group, the study aimed to investigate the social and psychological advances such a group can offer, and how this may contribute to psychosocial recovery following ABI. Also, the paper indicates how peer support groups may possibly have an impact on the everyday lives of adolescents and young adults with ABI.

Keywords: adolescent, young adult, acquired brain injury, psychosocial, peer support

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INTRODUCTION

According to a Danish study on incidence of acquired brain injury (ABI) in young adults between the age of 15 and 30, a total of 10,542 first-time hospitalizations were identified between 1994 and 2013, making an average of barely 1,200 per year (1). Despite this relatively low number of adolescents and young adults acquiring a brain injury, it is a significant group to consider, as these survivors will probably experience lifelong deficits in many different life areas. Individuals with ABI are usually confronted with a variety of challenges related to physical and cognitive impairments (2–4). It is evident though that the impact of brain injury depends not only upon the type and severity of symptoms, but also upon age at the time of injury onset (5, 6). Young individuals tend to have more unique psychosocial and supportive needs besides specific health concerns, and these issues range beyond physical and cognitive difficulties and include matters related to education, family establishment, relationships, and social activities (5, 7–9). Not only may a sudden and unexpected life event as acquiring brain injury have major implications regarding lifestyle, employment, and social life but additionally, young individuals might have to live with the consequences of injury for most of their lives, often with a dependency on rehabilitation services or instrumental and financial support. Individual concerns and priorities may be different from prior to ABI but furthermore, adolescents and young adults may be confronted with a profound diversion from their anticipated life trajectory (8). The relationship between sudden onset of severe illness and its psychosocial impact on the anticipated life trajectory can be defined by the sociological concept *biographical disruption* (10). By the concept of biographical disruption, it is further suggested that social support can play a significant positive role in adapting to a changed life situation and in regaining a sense of normalization, which is termed *biographical repair* (5, 10).

For adolescents and young adults with ABI, the probability of meeting like-minded peers in hospital settings is low. According to *The Danish Stroke Association*, the number of adults acquiring brain injury in Denmark is about 20,000 (11). Compared to the aforementioned 1,200 patients between 15 and 30 years, there seems to be a domination of older patients and thereby, neurology departments are likely to be dominated by elderly. Consequently, most rehabilitation services may be centered on problems and needs of these patients, and these might be quite distinct from the needs of young patients (6, 12). At the same time, individuals with ABI are often limited in socializing with peers, which could possibly be due to a disruption during education or work, eventually preventing study-related or collegial contacts (13). Moreover, a reduction in socially skilled behavior can be evident particularly following traumatic brain injury (14), and concerns of identity and social norms may arise, inhibiting or even preventing participation in social activities. In helping adolescents and young adults with ABI in obtaining biographical repair, it seems thus necessary to consider psychosocial needs and focus on regaining social abilities to possibly assist these young individuals on their way toward psychosocial recovery.

Peer Support

Research literature regarding peer support for adolescents and young adults with ABI is limited. However, there is a substantial body of literature indicating effectiveness of using experiential peers in other populations, including psychiatric patients and drug or alcohol addicts [see review by Solomon (15) and Repper and Carter (16)]. Since peer support has proven to be efficient in helping people get through difficult life situations [e.g., (17)], it is found relevant to investigate whether it can be beneficial for adolescents and young adults with ABI. In the literature though, different definitions of peer support are provided, indicating a lack of conceptual consensus. Typically, the term *peer support* defines interventions of social and emotional support offered by people with experience and characteristics similar to recipients (15, 18). Peer supporters are assigned or trained in providing support and can be either financially compensated or volunteers. The overall idea of peer support is letting individuals meet others who have gone through similar life events. Additionally, these like-minded peers can provide advice about strategies based on their own experience, as opposed to advice based only upon theoretical knowledge (17).

Mead and MacNeil (19) have listed some fundamental principles about peer support. These include peer support as not necessarily assuming a specific problem orientation, and as being about mutual responsibility and communication rather than assessment or evaluation, and as focusing on building relationships that support learning and growth. The roles of helper and helpee are not static in that peer support assumes full reciprocity. To supplement these principles, another frequently suggested aspect of peer support is the opportunity to benefit from helping others, traditionally termed *the helper-therapy principle* (20). This principle claims that not only the received help and support is beneficial, but also the act of supporting and helping. In this respect, helping and thereby having an impact on the lives of others may lead to enhanced sense of interpersonal competence and sense of self.

Previous research has suggested that peer support groups can increase social relations and quality of life, which on a societal basis may have economic benefits in the form of reduced number and length of hospitalizations (15). In the present paper, a specific peer support group is presented in which the concept of peer support encompasses the principles defined by Mead and MacNeil (19) and Riessman (20). Additionally, in the group presented here, there is emphasis on like-mindedness, and every participant is as much the supported as the supporting part. Thus, the group is bidirectional and reciprocal, since every participant constitutes a role of a helper *and* a helpee. Despite differences in how far participants have come in recovering from ABI, no one is regarded as more experienced or higher hierarchically placed, and none of them are trained or paid for participating. However, professionals with specialized knowledge about ABI have organized and led group meetings.

Young Brains—A Unique Peer Support Group

Young Brains (*Unge Hjerner*) was conducted as a subproject of the project, *National Study on Young Brain Injury Survivors,* Department of Neurology, Rigshospitalet, Denmark. Young Brains was established in January 2017 with a preliminary duration of 1 year. It was a social intervention with the aim of enabling individuals at the age of 15–30 with ABI to meet like-minded peers. The group constituted a possibility of sharing experience and practicing social behavior, while it had psychoeducational elements by which participants could learn about ABI and related subjects. Patients with affiliation to *The National Study on Young Brain Injury Survivors* in the capital region were invited to join the group. The meetings took place twice a month in a rehabilitation center, and young individuals with ABI were free to participate without specific requirements or commitments.

The concept of Young Brains was not offering therapy *per se* but was rather meant as a supplement to ordinary rehabilitation. For that reason, participants with specific questions related to rehabilitation services, facilities or similar were advised in seeking such through the right channels. A case manager and two neuropsychologists organized and planned meetings, facilitated group discussions, and offered learning opportunities. The content of the meetings alternated between socializing, experience sharing, and presentations by guest speakers with theoretical knowledge related to ABI and youth. Every meeting had a theme and was described in a program sent out for the whole season (themes are listed in **Table 1**). The meetings always

TABLE 1 | Themes of the young brains meetings.

Meeting	Theme
1. Socializing	
2. Presentation with ABI-related content	Presentation by a medical doctor and a physiotherapist: *Physical training after brain injury: advice, possibilities and limitations*
3. Socializing	
4. Presentation with ABI-related content	Presentation by a well-known Danish neuroresearcher: *The Brain*
5. Socializing	
6. Presentation with ABI-related content	Presentation by a social worker from a job center: *Meeting the local authority*
7. Socializing	
8. Presentation with ABI-related content	Presentation by a neuropsychologist from a rehabilitation center: *Who am I now? – About identity and brain injury*
9. Socializing	Creative activity with an artist (*Unmasking brain injury*)
10. Presentation with ABI-related content	Presentation by an occupational therapist: *Apps for training and daily help*
11. Socializing	Evaluation

started with an introduction round in which all participants were asked to present themselves by name and age, and they were invited to elaborate as much as they felt like about their brain injury. Also, they were encouraged to raise specific themes for that particular meeting, if they had any in mind. After the introduction round, the participants chose themes they wanted to discuss more thoroughly. Besides group discussions, at some meetings a guest speaker was invited to present a relevant topic about being a young survivor of ABI. At the end of all meetings, participants were asked if they had any questions, and the theme and program of the next meeting was presented.

The Present Study

The present study aimed to evaluate and illuminate how a peer support group was received by participants, and how they perceived the effects of participating on their everyday life.

METHODS

Participants

Participation in the Young Brains group required former or current affiliation to *The National Study on Young Brain Injury Survivors*, a national project in which an age interval of 15 to 30 years was required by the Danish Ministry of Health. Therefore, all participants in this study had been affiliated to the project and at time of the current study, they were between the age of 19 and 32. At the time of data collection, all participants had mild to moderate difficulties related to the ABI. Specific injury related data and data concerning rehabilitation was not collected as a part of the study, as it was conducted in the chronic phase after injury.

Settings and Procedure

Quantitative and qualitative approaches were combined in the current study, using both questionnaire and interviews. Before producing the questionnaire and the semi-structured interview guide, a psychologist observed the Young Brains group during three meetings to obtain information about the group and the procedure. The study period was from May to mid-June 2017.

A link to an online questionnaire was sent to all participants in the Young Brains group. Five of them were further invited to participate in a semi-structured interview, whereof four agreed on being interviewed. The respondents were selected based on gender, age, participation frequency and time since injury onset. These criteria were set to make sure respondents represented the diversity in the group as much as possible despite the limited number of respondents. The four respondents participated in most of the meetings (half of the meetings or more), so they were familiar with the structure and procedure of the group. The interviews took place one-on-one, either in the out-patient clinic at Rigshospitalet, Glostrup or in the respondents' own homes, and every participant was interviewed once.

Questionnaire

The questionnaire of 21 questions was sent out to all participants of Young Brains with a description of the aims of the questionnaire and information regarding how responding was optional and anonymous. The full questionnaire is listed in a translated version in **Table 2** and was structured as follows:

Part 1: Demographic information, including gender, age, time since injury, and employment, which enabled examination of pertinent features of the participants.
Part 2: Frequency of participating in meetings and reasons of participating.
Part 3: Participants were asked for their opinion of the different ABI-related presentations.
Part 4: This part was about socializing in the group and consisted of a list of statements, where participants were to select between five levels of agreement. These statements were formulated to explore participants' opinions about Young Brains.
Part 5: Open-ended questions such as what was the best part of Young Brains, if they got anything usable for their everyday life, and what they would change if possible.

Semi-Structured Interviews

A semi-structured open-ended strategy was used in the interviews to allow participants to freely elaborate on their experiences and opinions, which also enabled capturing the unique verbal accounts of the respondents. Initially, they were introduced to the aim and were asked for permission of audio-recording to transcript the responds for later analysis. The duration of the interviews was 30–40 min, and respondents could ask for breaks when needed. The interviews were based on an interview guide, divided into nine sections with distinctive themes, structured as follows:

Part 1: Demographic information was obtained in the same order as in the questionnaire.

TABLE 2 | Questions from the questionnaire (translated from Danish).

Themes	Questions
1. Demographic questions	1. *What is your gender?* – *boy/man* – *girl/woman*
	2. *How old are you?* ____________
	3. *When did you acquire your brain injury?* – *0–1 years ago* – *1–5 years ago* – *5–10 years ago* – *10 years ago or more*
	4. *What is your situation of employment?* – *Studying* – *Working* – *On sick leave* – *Unemployed* – *- Other* ____________
2. About the meetings	5. *How many times have you participated in Young Brains?* – *Every time* – *Most of the times* – *Half of the times* – *A few times* – *I have not participated yet*
	6. *Why do you participate in the meetings? (choose one or more)* – *To meet others with ABI* – *To hear the presentations from professionals* – *To get away from home* – *Because others tell me to go* – *To get some advice on how to handle specific problems* – *Because it is nice to be there* – *To tell my own story* – *To hear the stories of others* – *Other* ___________
	7. *Please state below how well you think the statements fit the Young Brains group (likert-scale with six degrees of agreement, ranging from "Totally right" to "totally wrong")* – *A good support* – *A good way of sharing experiences* – *A good way to hear how others handle their situation* – *A chore* – *A break from everyday life*
	8. *The program of Young Brains changes from time to time between socializing and ABI-related content. What do you think of this distribution?* – *Not enough socializing and too much ABI-related content* – *Not enough ABI-related content and too much socializing* – *- The distribution is fine*
3. ABI-related content and presentations	9. *State below your degree of agreement in the following statements (likert-scale with six degrees of agreement, ranging from "totally disagree" to "totally agree")* – *The presentations have been relevant for me (every single theme/presentation was listed)*
	10. *Did one of the presentations make a certain impression on you?*
	11. *Why did this particular presentation make an impression on you?*
4. Socializing	12. *State below your degree of agreement (likert-scale with 5 degrees of agreement, ranging from "totally disagree" to "totally agree")* – *The participants in young Brains understand me better than my peers* – *I dare to tell about personal worries and problems in Young Brains that I do not tell others about* – *I feel a greater support in the group than elsewhere* – *I get inspired when I hear how other group members handle their problems* – *I get inspired when I hear others in the group tell about their accomplishments* – *By attending to the meetings I have become better at telling about my injury* – *I talk to others in the group about things that I do not talk to others about*
	13. *Have you had any contact to other participants in private?* – *Yes* – *No* – *No but I would like to*
	14. *Have you had any contact to other participants via SMS, Facebook, or similar?* – *Yes, frequently* – *Yes, one or a few times* – *No* – *- No but I would like to*
	15. *Are you a member of the Facebook group "Young Brains"?* – *Yes* – *No*
	16. *How often do you visit the Facebook group?* – *Daily* – *Weekly* – *Monthly* – *Rarer*
	17. *What do you use the Facebook group for?* – *To be reminded of meetings* – *To communicate with others in the group* – *- I do not use the Facebook group*
6. Ending and your comments	18. *What do you think is the best part of Young Brains?* ___________
	19. *Do you think Young Brains give you anything usable for your everyday life? (please describe below)* ___________
	20. *Is there anything about Young Brains that you wish could be different? (please describe below)* ___________
	21. *Do you have any ideas about potential future themes, presentations etc.?* ___________

Part 2: Structure of Young Brains, including opinions on location and frequency. It also involved questions about the concept of professionals leading discussions.

Part 3: Participants' opinions on the Young Brains program, including the distribution between socializing and learning via professional presentations.

Part 4: Reasons for participating in the group were investigated.

Part 5: Benefits of participating and asked whether anything in the group was not present in other social settings, and if being there was different from being with peers in general.

Part 6: Support and understanding in the group setting compared to personal networks.
Part 7: Sharing experiences.
Part 8: Impact of Young Brains on their everyday lives was investigated, including whether they expected their situation to be different without the group. Also, benefits for everyday life, and changes in their ways of talking about ABI after participation.
Part 9: Young Brains were to be described in three words. In addition to this, participants were asked about the best thing about the group and also, what could possibly be better.

When all questions were answered, participants were encouraged to add points that were not covered throughout the interview. The audio-recordings were transcribed verbatim, and names or potentially identifiable information were anonymized. The transcripts were read multiple times and notes of significant statements were conducted.

ETHICS

The study was conducted in accordance with the Helsinki Declaration. All participants were informed orally and in writing about the purpose of the study, and written consent to participate and to publish data was obtained from all of them. Due to Danish legislation, ethics approval was not required for the present study.

RESULTS

Results From the Questionnaire

The questionnaire was completed by 17 participants, including 5 males and 12 females.

Participant Characteristics

Participant characteristics are listed in **Table 3**. The gender distribution was a majority of females (12 out of 17). The age range for the participant group was 19–32 years, making an average of 25.5 years. Out of the 17 participants, 12 were within 5 years of injury onset, and four out of these 12 participants were within 1 year. In relation to employment, eight were studying and one was employed at the time of the study (not further specified). The remaining eight participants were unemployed, early retired, or on sick leave. Regarding frequency of participation in the Young Brains meetings, 13 had participated in half of the meetings or more, while the remaining four had participated in less than that.

Reasons for Participating in Young Brains

Participants were asked to choose one or more reasons of participating in Young Brains among eight options. As is seen in **Table 4**, all participants chose the option *To meet other young individuals with ABI*. Other reasons commonly selected were *To get advice on how to handle specific problems* (15) and *To listen to professional presentations* (15). No one stated that others told them to go.

TABLE 3 | Characteristics of the participants.

Gender	Age	Time since injury	Employment at the time of the study	Participation in meetings
Female 76% (12)	19–21 29.5% (5)	<1 year 23.5% (4)	Studying 47% (8)	All times 11.5% (2)
Male 24% (5)	22–24 17.5% (3)	1–5 years 53% (9)	Employed 6% (1)	Almost all times 47% (8)
	25–27 17.5% (3)	6–10 years 11.5% (2)	Unemployed, early retired, on sick leave 47% (8)	Half of the times 17.5% (3)
	28–32 35% (6)	>10 years 11.5% (2)		A few times 17.5% (3)

TABLE 4 | Reasons for participating in young Brains.

Responding options	Percentage of times chosen (%)
To meet other young individuals with ABI	100
To get advice on how to handle specific problems	88
To listen to the professional presentations	88
Because I like the atmosphere	76.5
I want to hear the stories of others	65
It feels good to tell my own story	47
To get away from home	18
Others tell me to go	0.00

Participant Benefits

To investigate benefits of Young Brains, participants were asked to rate their degree of agreement on eight statements. The highest level of agreement was on statements describing Young Brains as *A great support*, *A good way of sharing experience*, and *A good way of hearing how others handle their situation.* No one responded with the rating of Young Brains as being *A chore*. Other results reveal that most of them felt more understood and supported by peers in the group compared to other social networks. The majority of participants (13 out of 17) stated that they could talk about personal concerns and problems in the group that they did not tell others, and 13 also replied that participation made it easier to talk about their brain injury elsewhere. When asked if Young Brains had had any benefits in everyday life, participants replied in a free text box. One mentioned courage and perspective: *"It gives me courage to move on and continue fighting in my everyday life. It helps me to see things from another perspective [...]"* (m, 21). Another highlighted understanding: *"I get help dealing with challenges that weigh heavily on my shoulders and are hard to explain to others. With them I don't have to explain for 15 minutes – the understanding is there right away. That's a relief; it calms me down."* (f, 26). Others wrote how they had become more open and accepting about the consequences of their injury.

RESULTS FROM THE INTERVIEW

Participant Characteristics

Four participants ($m = 2$, $f = 2$) were interviewed. Since completing the questionnaire was anonymous and sent to all participants in Young Brains, respondents might possibly have participated in both the questionnaire and the interview. Characteristics of the respondents at the time of the interview are listed in **Table 5**.

Reasons for Participating in Young Brains

The respondents were asked why they initiated participating in Young Brains, and why they continued to participate. All respondents stated the main reason as a need of meeting like-minded peers as both the reason of initiating and continuing participation. One respondent further elaborated *"It originated in my need of finding a place to fit it"* (R4).

Themes

In analyzing the interviews, three principal themes were identified, each with three corresponding subthemes as illustrated in **Table 6**.

Socializing

A Supportive Network

Most respondents stated having great supportive networks, but did not feel truly supported or understood by them. One respondent uttered: *"I think family and friends support me as well as they can, but when the real understanding isn't there, it's difficult"* (R2). In general, respondents had difficulty in talking to friends and family about the injury, which often amplified feelings of loneliness and disconnecting from emotional and social support. Some avoided talking about their injury and did not want to bother their relatives who were already personally and emotionally involved. As a result, respondents had rarely spoken about injury-related concerns, and most of them had not openly expressed their worries and frustrations before participating in Young Brains.

All respondents stated profound differences on the support provided in Young Brains compared to other networks. *"They understand what's difficult and what the closest friends don't understand [. . .]. Well, my friends try but I can feel it's not the same."* (R2). Respondents described Young Brains as a supplement to family and friends, and all stated that the group made them feel more supported and understood than in other networks. They described Young Brains as offering more authentic in-depth feelings of support, and because acknowledgment and feedback was given from like-minded peers, they felt a higher and more significant value of the support.

TABLE 5 | Respondent characteristics.

Respondent	Gender	Age	Employment
R1	Male	21	Studying
R2	Female	32	Employed (part time)
R3	Male	23	Employed (full time)
R4	Female	31	Studying

TABLE 6 | Themes and subthemes identified in the interviews.

Core theme	Subthemes
Socializing	A supportive network Mutual and reciprocal understanding A place to belong
New knowledge	Motivation, inspiration and collective problem-solving Professional guidance Practicing skills in a safe environment
Psychosocial well-being	Relief of concerns Accept and normalization Sense of purpose and social value

Mutual and Reciprocal Understanding

Respondents expressed difficulty in relating to even close relatives following ABI. They felt challenged by the invisibility of their injury and often had to explicate how they could not do the same things to the same extent as before, as in the following example: *"I cannot stay out until 3:AM anymore and they don't really understand. And they often put pressure on me, right? They say "Are you leaving early again?" and things like that."* (R3). Most respondents had even experienced people doubting on the consequences of ABI, and some mentioned this as both impeding participating in social activities and as changing their social relationships. Two respondents explained how they did not perceive their relationships with friends and family as reciprocal anymore, and one of them opposed this to his experience in Young Brains: *"In Young Brains we are all equal. No matter what our background is. It's our illness that ties us together. I don't consider anyone better than others* [. . .]. *We're all equal"* (R1). He felt a connection due to reciprocity and continued: *"On the outside I look like a completely normal guy and nothing is wrong with me. But everyone in Young Brains knows. It's on the inside something's wrong."* (R1).

In general, respondents could relate and understand their peers in Young Brains, and when sharing individual accomplishments, they felt like overcoming challenges together. One respondent explained her way of relating to the victories of others: *"It's nice to go somewhere where people understand the upturn swell of reading 40 pages in a row or something. Maybe they don't understand exactly about the 40 pages, but they can hear the way I'm telling it and they can translate it to their own injury. Another participant once said "I've cut over an avocado on my own." [. . .] You can feel it in the way she tells it – Hey, that's like when I read my book!"* (R4).

A Place to Belong

None of the respondents had previously encountered peers in similar situations. Confronted with completely changed life situations, it was hard to find their place when being with others, and through observation at group discussions it became clear, how the participants faced new challenges and contrasts to the lives they lived before. For all respondents in the study, Young Brains constituted the first meeting with like-minded peers, which made them discover that they were not alone in being a young survivor of ABI. Participants found a place to fit in and be accepted both despite and in virtue of being young with ABI.

New Knowledge

Motivation, Inspiration, and Collective Problem-Solving

Respondents felt motivated by each other. By listening to how peers handled individual challenges, they felt encouraged to try something alike to handle theirs. Some participants stated that telling about accomplishments increased their self-confidence and enhanced their motivation. They found it inspiring, motivating and instructive to hear about the challenges of others, and some even saw individual accomplishments as common victories: *"I think we all get happy when hearing about the success or fight of another person. In a way we have been on the sidelines and seen the fight and then… Who wouldn't be happy when a person comes back and tells you that he won that fight?"* (R1). Thus, it was not only inspiring to hear about specific problems but also to just listen to peers telling it was possible to overcome struggles.

Related to sharing experience, one respondent expressed the following: *"Maybe you come up with five tools of handling your problems, but after two hours in the group, you'll have five or six new"* (R1). Another had a similar experience of seeking advice in the group: *"When you say "I find it hard to settle down and I can't sleep" or something, they give you like eight options of what to do[…], and there are no hard feelings about using the advice or not."* (R4). The group was used as a way of gaining motivation and courage to face challenges, and not least as a forum of collective problem solving where specific problems and potential solutions could be discussed.

Professional Guidance

All respondents in the study expressed an importance in professionals organizing the meetings. One stated reason for this was that it enabled a more objective viewpoint as a supplement to participants' subjective experiences. However, it cannot be concluded whether participants would have a similar experience with a different group design or in another setting. More than focusing on neurological and physical impairments, the professionals of Young Brains had a focus on both brain processes and potential consequences of this however, they also emphasized a focus on issues concerning adolescence and young adulthood.

Practicing Skills in a Safe Environment

The interviews reveal that new knowledge was not only gained through listening to peers and professionals. Participants used the group to practice social and communicative skills, and when asked if participation had any impact on their way of talking about their injury, they all replied that it was easier to talk about their injury after discussing it in the group. By talking freely about it there, they did not make a big deal of talking about it in general. Some participants were convinced that discussions in Young Brains made them more open about their situation and more able to accept it. They practiced how to put their own situation into words and to talk about it without being emotionally overwhelmed. One respondent described how sometimes she felt even too open and straightforward: *"Sometimes I get into situations, where it's easy to say "Well, that's just because I had two strokes," and people are like "Excuse me, what did you say? Aren't you dead then?", but anyway I think it's a relief to have come so far that I can tell it in that way."* (R4).

Psychosocial Well-Being

Relief of Concerns

One respondent was uncomfortable about talking to relatives about his injury, but he had no problem of mentioning it in Young Brains, where he could freely express worries and thoughts of guilt or frustration. Another one explained how she had removed injury-related concerns from everyday life by letting it out at the meetings. She used Young Brains as a kind of parking lot for issues related to the injury, with the result of her everyday life not being overshadowed by negative thoughts and worries. In Young Brains she could place more and more of her injury-related thoughts, thereby diminishing it from other settings and relations. In the interview, she elaborated her need of having a place where *it* could be, with *it* referring to her injury: *"For me it's about having somewhere, where **it** has a place […]. That part of me filled everything once and had no place to be. That part of me is no longer that big, but that part of me – I still need it to have a place somewhere. I don't want it to fill my whole everyday life, and that's why it's nice to have somewhere to go, where **it** can be"* (R4).

Accept and Normalization

Respondents described their lives as drastically changed after their injury. They were challenged by impairments and had concerns related to the question: Who am I now? One respondent described a need of peers to share experiences with, thereby being validated, as this anecdote about delivering an examination paper illustrates: *"I felt sick for like one and a half weeks afterwards. I couldn't understand what happened, and then we got to talk about energy management and fatigue and about spending energy […]. When we talked about it, I understood, and it made sense, and then I didn't understand how I couldn't have understood. One is just firmly anchored in a "before I got ill"-understanding of oneself […]."* (R4). By talking to peers in Young Brains, she gained a comprehensive explanation of why she felt as she did and could accept it better. She further highlighted that meeting like-minded peers gave her a real and credible base of comparison: *"It's important for me to have a perspective. If I were to compare myself with people that do not have a damage to the brain, I'm just bad at everything"* (R4). Others also mentioned the opportunity of viewing their situation from new perspectives. They met peers with similar or even more challenging issues, which made them reflect on their own situation, though some also felt ambivalence when listening to peers with more significant or visible impairments. Comparing oneself with others generally had a positive impact and constituted a way of challenging beliefs about ABI. Further, it contributed to a sense of normalization and a greater acceptance of their situation.

Sense of Purpose and Social Value

An important benefit gained from Young Brains was a feeling of helping others. By sharing personal stories, successes and challenges, respondents inspired each other to face challenges, which contributed to a sense of empowerment. When asked if they felt like helping others, all replied that they did not do anything special, though most of them had been told that something they said was helpful. Helping others contributed to convictions that their experiences were helpful for others. According to this, one respondent said: *"In a way it's about having experiences that have costed so much, right? [. . .] In a way you need it to help somewhere in the world, right?"* (R4).

DISCUSSION

The aim of the study was to evaluate and illuminate how a peer support group was received by a group of young ABI survivors, and how they perceived the effects of participating on their everyday life. There was no data collection before participating in the group why it cannot be concluded whether the group *per se* made a difference for participants. However, based on the results, tentative conclusions are discussed in terms of how peer support groups could possibly contribute to fulfilling psychosocial needs and thereby assist adolescents and young adults with ABI on their way toward psychosocial recovery.

Hit in the Heart of Life

When acquiring a brain injury during adolescence or young adulthood, the individual is figuratively speaking "hit in the heart of life," meaning drastic disruptions and significant deviations from their anticipated life trajectory, and in a time where they are usually not yet settled, when it comes to family, education, career, etc. Peer support has proved valuable in many populations, and the current study indicates how it may also be beneficial for young ABI survivors. Being young with ABI may induce a variety of concerns and challenges related to finding oneself in a drastically changed life situation, but they are often left alone to fulfill psychosocial and supportive needs. Prior research has claimed that peer support can enhance social networks and increase quality of life [see review: (15)] and is suggested to fulfill emotional and social needs after unexpected neurological events (21, 22). This seems consistent with the findings in this study.

Are Peer Support Groups More Beneficial Than Other Social Networks?

Adolescents and young adults with ABI rarely meet patients of their own age. For most participants in this study, Young Brains was their first meeting with peers with ABI, and the results of the questionnaire and interviews equivocally reveal the main reason of participating in the group was meeting like-minded peers. Having a place to express worries and thoughts and have it acknowledged by peers fostered feelings of not being alone. Moreover, receiving feedback and understanding from peers seemed to make participants feel validated on their experiences and difficulties. Participants in the group felt understood and supported in ways they did not feel elsewhere, even if they had supportive social networks. Based on the interviews supplied with results from the questionnaire, it is revealed that participants felt free to talk about personal issues, and they did not have to explain or defend themselves, possibly because they were met by reciprocal and like-minded peers. Thus, according to the results, peer support groups can possibly have beneficial psychosocial elements for adolescents and young adults with ABI. This is consistent with prior research on peer support groups showing positive outcomes on various psychosocial constructs, including self-confidence, adaptation to disability etc. (5, 23, 24).

Can Peer Support Groups Reduce Social Isolation?

Social isolation is a frequent consequence of ABI. Previous research suggests that peer support groups can play a role as a social gathering and replace limited or even lost social opportunities (5), which seems to be confirmed in this study. Participants in this study could test their own limits and which considerations to take in social settings. Thereby the group constituted a safe environment to develop social and communicative abilities without being judged or stigmatized. The group did not require much more from participants than showing up, and respondents from the interviews emphasized a clear understanding of fatigue, lack of resources, etc. Consequently, participating in the group was considered participating in a social activity on their own terms. This clearly played a role in how participants talked about themselves and their brain injury in general. By telling their stories and sharing challenges and accomplishments in the group, not only did their relation to each other grow, but they also practiced how to express themselves and communicate with others. Accordingly, the group might have contributed to development of social abilities and thereby constituted a way of reducing the risk of social isolation.

How Can Participants Benefit From Each Other?

Participants expressed how they motivated and inspired each other and benefitted from the experiences of others. In the questionnaire, it was stated specifically that they participated to hear others tell their story rather than to tell and share their own story. Respondents from the interviews claimed to be introduced to new ways of thinking and increased courage to face challenges, but the group also contributed to a sense of meaning and value when sharing experiential advice, consistent with the helper-therapy principle (20). Participants felt like gaining a sense of empowerment and social value since they were contributing to the recovery and well-being of others. Furthermore, personal experiential knowledge made it possible to use the group for collective problem solving in the sense that participants raised questions about specific issues, and peers made suggestions on how to deal with it. Thus, problems were collectively discussed, and concurrently the successes of individuals were perceived as common victories. However, the study did not measure whether these experienced benefits reflect real changes in the lives of the participants, but only their subjective descriptions of their experiences of participating in the group.

Does Participation in a Peer Support Group Have an Impact on Everyday Life?

In investigating whether peer support groups can contribute to psychosocial recovery, an important question is whether participation affected the everyday lives of participants. Based on the results, the answer to this question is clearly positive. Our method do not allow us to conclude, but the results from the questionnaire reveal high degrees of agreement on statements saying that they learned new strategies of dealing with ABI, they found a place to fit in and felt understood and supported. The interviews further revealed that respondents became part of a reciprocal network, made friendships, and gained a sense of social value. However, a very important profit of the group was an increased accept of their situation. By meeting like-minded peers, they got a reliable basis of comparison; they got to see themselves from new perspectives and were challenged on their beliefs. Moreover, the group served as a place to put injury-related issues, thereby eliminating it from everyday life. Whereas, support groups may be perceived as beneficial, it is not yet proven that they do provide a step toward well-being in everyday life.

How Can Peer Support Contribute to Psychosocial Recovery?

Respondents from the interviews reported that they often felt alone and avoided talking to relatives about injury-related concerns. They found it hard to relate to peers on one side and to ABI patients on the other, since many of them had not met any patients of their age before. Participants felt a special connection to each other and felt understood and supported in distinct ways, compared to other networks, which was also confirmed by the results of the questionnaire. Also, participants were inspired and motivated to try out new strategies of handling challenges, and they practiced social and communicative abilities. They learned to view themselves from new perspectives and got reliable basis of comparison. More of them stated that they had become more open about their injury and got to accept their situation. Moreover, a part of the concept of Young Brains was to provide psycho-educative features. By listening and asking, participants clearly gained knowledge about ABI and youth. Thus, following an ABI-induced biographical disruption, a peer support group may contribute to biographical repair and thereby to some degree of psychosocial recovery.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

Though this study indicates that peer support groups might be beneficial for psychosocial recovery following ABI, young ABI survivors with behavioral difficulties could potentially have inhibitory impact on group discussions. Further, it may not be as beneficial in the acute phases of injury, since participating may be quite demanding for newly injured individuals due to medical matters, fatigue, existential crisis, etc.

The group was found to be highly dependent on professionals with experience from ABI treatment to organize and lead meetings. Their role was not only planning but also to form a frame and frequently explicate this, which included facilitating participation with specific focus on guiding and supporting participants with behavioral or other barriers for participation, related to their ABI. It was further revealed that participants had a need of contact to the professionals between meetings to ask clarifying questions.

When it comes to considerations on location, some individuals with ABI have physical difficulties why location for group meetings may include availability for wheelchairs and people with impaired mobility. Also, participants in this study stressed the importance of easy access by car and public transportation.

Limitations in This Study

Originally, the data collection of this study was completed in order to evaluate Young Brains as a social intervention. Therefore, the questionnaire and the interviews were centered on questions on the intervention *per se*, and on the yields of this specific group design. This means that there is no data collected from before participating in the group and thereby no such data for comparison. Moreover, detailed participant characteristics were not collected as part of the not addressed in this study.

The results of this study are based on the experiences of a small group of young ABI survivors ($n = 4$ in the interview and $n = 17$ in the questionnaire). These participants actively participated in the intervention for several months and thus, results are based on experiences and reflections from participants, who were positively minded and who generally found the intervention meaningful and beneficial. Therefore, one has to be careful to generalize findings, and there is still a need of research focusing on the characteristics of young ABI survivors, who might benefit from this kind of intervention.

CONCLUSION

Peer support groups might play a significant role in assisting adolescents and young adults with mild to moderate ABI toward psychosocial recovery. Young ABI survivors are often drastically disrupted in an age and life stage that is already quite unsettled and demanding, in other words hit in the heart of life. This study reveals insight in how meeting like-minded peers may be beneficial by enhancing psychosocial adjustment of adolescents and young adults with ABI. Thus, age-appropriate peer support groups could possibly fulfill a special role not usually met in the structure of rehabilitation services, though more research is needed on this topic. Participants in this study experienced they could provide comprehensive understanding and support to each other that was not found elsewhere. However, there is also still a need for research that provides more knowledge as to what characterizes patient groups, who could profit from this kind of intervention. Furthermore, we lack knowledge of whether peer support groups actually influence other parameters than self-perceived outcome.

ETHICS STATEMENT

The study was conducted in accordance with the Helsinki Declaration. All participants gave written consent to participate.

AUTHOR CONTRIBUTIONS

AN, BF, and LB contributed conception and design of the study. LB formulated the questionnaire and the interview guide, collected and analyzed data. LB wrote the first draft of the manuscript. AN and BF wrote sections of the manuscripts. All authors contributed to manuscript revision, read and approved the submitted version. The corresponding author takes primary responsibility for communication with the journal and editorial office during the submission process, throughout peer review and during publication. The same author is also responsible for ensuring that the submission adheres including details of authorship, study ethics and ethics approval, etc. The corresponding author should also be available post-publication to respond to any queries or critiques.

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REVIEW
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Randomized Controlled Trials of Rehabilitation Services in the Post-acute Phase of Moderate and Severe Traumatic Brain Injury – A Systematic Review

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Background and aims: There is a gap in knowledge regarding effective rehabilitation service delivery in the post-acute phase after traumatic brain injury (TBI). Recently, Gutenbrunner et al. proposed a classification system for health-related rehabilitation services (International Classification System for Service Organization in Health-related Rehabilitation, ICSO-R) that could be useful for contrasting and comparing rehabilitation services. The ICSO-R describes the dimensions of Provision (i.e., context of delivered services), Funding (i.e., sources of income and refunding), and Delivery (i.e., mode, structure and intensity) at the meso-level of services.
We aim to:
-Provide an overview of randomized, controlled trials (RCTs) with rehabilitation service relevance provided to patients with moderate and severe TBI in the post-acute phase using the ICSO-R as a framework; and
-Evaluate the extent to which the provision, funding and delivery dimensions of rehabilitation services were addressed and differed between the intervention arms in these studies.

Materials and methods: A systematic literature search was performed in OVID MEDLINE, EMBASE, CINHAL, PsychINFO, and CENTRAL, including multidisciplinary rehabilitation interventions with RCT designs and service relevance targeting moderate and severe TBI in the post-acute phase.

Results: 23 studies with 4,644 TBI patients were included. More than two-thirds of the studies were conducted in a hospital-based rehabilitation setting. The contrast in Context between the intervention arms often co-varied with Resources. The funding of the services was explicitly described in only one study. Aspects of the Delivery dimension were described in all of the studies, and the Mode of Production, Intensity, Aspects of Time and Peer Support were contrasted in the intervention arms in several of the studies. A wide variety of outcome measures were applied often covering Body function, as well as the Activities and Participation domains of the International Classification of Functioning, Disability, and Health (ICF).

Conclusion: Aspects of service organization and resources as well as delivery may clearly influence outcome of rehabilitation. Presently, lack of uniformity of data and collection methods, the heterogeneity of structures and processes of rehabilitation services, and a lack of common outcome measurements make comparisons between the studies difficult. Standardized descriptions of services by ICSO-R, offer the possibility to improve comparability in the future and thus enhance the relevance of rehabilitation studies.

Keywords: rehabilitation, services, traumatic brain injury, randomized trials, post-acute

BACKGROUND

Traumatic brain injury (TBI) is a worldwide public health problem and can result in long-term disability (1–3) with the need for extensive and highly specialized initial health care provision, followed by comprehensive rehabilitation efforts (4). Physical, cognitive and emotional problems, including inability to return to full- or part-time work, as well as diminished quality of life, are frequent long-term consequences of TBI. Effective delivery of rehabilitation services and integration of medical perspectives, as well as vocational, educational and community support, are deemed necessary to meet the complex needs of this population. Services derive from the act of serving and refer to the provision of intangible products offered to persons with health conditions. Rehabilitation services in particular imply strategies targeting subsequent disability (5). Service delivery can be viewed from societal, institutional and individual perspectives. These different levels are often referred to as macro-level, including policy and financial aspects, meso-level, including organization and availability of services, and micro-level, including accessibility and content of services provided to an individual patient (6). Donobedian (7) described the quality of services as a causal relationship among the attributes of setting, the process of care, and the outcome. Evaluating the quality of rehabilitation services is important at every level, but the complexity of services and hence the challenges of evaluation can increase when moving from the micro- to the meso- and macro-levels.

A wide variety of rehabilitation interventions have been developed and evaluated with respect to content and outcomes for different functional problems after TBI (8). Service delivery to patients with severe TBI has focused on the acute phase, underpinning the importance of early initiated and well-organized delivery (9–11). Less is known about effective rehabilitation service delivery in the postacute and later phases, at least for the general TBI population (12, 13) and reviews focusing on this issue are warranted (14). Furthermore, the structure and process of care are seldom described, although they clearly impact the outcomes of TBI (15). The lack of a framework for depicting differences in service delivery could contribute to the scarce knowledge regarding optimal rehabilitation service delivery. Recently, Gutenbrunner et al. (16) proposed a classification for rehabilitation services, the International Classification System for Service Organization in Health-related Rehabilitation (ICSO-R), describing the meso-level of heath care. The ICSO-R is based on three dimensions Service provision," Funding and Delivery each of which has a more extensive list of categories and subcategories that characterize rehabilitation services (17). The classification builds on the conceptual framework by Meyer et al. (5) describing health-related rehabilitation services according to their organizational setting including technical and human resources in addition to their goals.

The classification was developed in order to cover the gap between classifications at the micro and macro level of health care exemplified by the International Classification of Functioning, Disability and Health (ICF) (18) and the International Classification of Health Accounts (ICHA) (19). The ICSO-R intended to provide tools for analyzing provision and delivery of rehabilitation services. Based on these assumptions the classification might also be useful for contrasting and comparing rehabilitation services across different care facilities at the local, regional and country levels. Thus far, the lack of framework has hampered a systematic approach to the service aspects in the existing rehabilitation literature and how these aspects influence outcomes (20). There is an urgent need for prognostic models in TBI facilitating comparative audits of services among hospitals, other health care settings and countries (21). The Service provider dimension of ICSO-R describes the framework of the institution, organization, the resources and quality assurance and could be applied to evaluate where, by whom and in which context the service is delivered. The Funding dimension describes the main sources of income and funding of the services (i.e., diagnosis-related groups, per-day payment or other forms of services refund.). Finally, the Delivery dimension contains the main strategies (i.e., preventive, curative, rehabilitation, supportive or other strategies) delivered to the users, aspects of intensity and duration of intervention and the way the service is organized, and can be used in order to evaluate what, for what and how the services are delivered (17). Hence, the ICSO-R may serve as a tool for such comparative audit.

Using the ICSO-R as a framework, the current review aims to provide an overview of randomized, controlled trials (RCTs) with rehabilitation service relevance provided to patients with moderate and severe TBI in the post-acute phase and to evaluate the extent to which organizing, funding and providing of rehabilitation services were addressed.

MATERIALS AND METHODS

A systematic literature search was conducted to identify controlled trials evaluating the effects of rehabilitation services or rehabilitation interventions with service implications.

INCLUSION CRITERIA AND DEFINITIONS

Studies targeting adults (>17 years old) with moderate or severe TBI and providing rehabilitation following the acute phase were included. TBI was defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (22). "Following the acute phase" was defined as rehabilitation occurring after discharge from the trauma center/acute-care hospital. A multidisciplinary approach was defined as at least two professions involved directly in the delivery of the intervention. Service relevance was operationalized to differences in the delivery, funding, or provision of the services between the intervention arms in the studies. A librarian was consulted to elaborate a thorough search strategy. Potential articles of interest in the English language were identified through a systematic search of the Medline (OVID), EMBASE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) databases (November 2016) with updated searches for 2016 through July 3, 2018, revealing a total of 2,970 hits (**Appendix 1**). In order to retrieve the highest possible number of relevant articles two filters were applied: the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) (https://training.cochrane.org/handbook); and the best balance of sensitivity and specificity filter for Therapy. These strategies build on optimizing the thesaurus terms, and adapted to the individual databases as recommended http://handbook1.cochrane.org. http://hiru.mcmaster.ca/hiru/HIRU_Hedges_home.aspx#Hedges. These filters were combined with "OR" in the search strategy in order to increase the number of hits. The filters were applied to the Medline and EMBASE searchs, but not in the search in the other databases. Hence these filters are assumed to increase and not limit the relevant hits.

REVIEW PROCESS

The titles of the 2,970 studies were screened for eligibility, with supplementary evaluation of the abstracts when necessary (238 studies). A total of 88 studies were identified as candidates. These studies were evaluated independently by two of the authors regarding fulfillment of the inclusion criteria, and when in doubt, full-text manuscripts were assessed. Based on consensus 46 studies were found to meet the inclusion criteria. In 23 of the studies the sample size was lower than 60. Inter individual variations in functional outcomes vary across the specific outcome measures and so do the power estimates for needed number of patients. However, power around 80% and with detection of group differences around half the standard deviation is often recommended (23). Thus, studies with n<60 were excluded *post-hoc* in order to avoid studies with too low power. Hence, 23 studies were included in the final analyses (**Figure 1**).

QUALITY EVALUATION

The quality of the studies was evaluated by three researchers according to their adherence to the CONSORT guidelines (24) and was scored according to the Cochrane recommendations (25). Risk of bias in the included studies was assessed in 12 domains: adequate randomization method; concealed allocation; blinding of participants; blinding of care providers; blinding of outcome assessors; dropout rate described and <20% for short-term and 30% for long-term outcomes; intention to treat, i.e., all participants were analyzed according to their randomized group allocation; unselective reporting, i.e., results were provided from all prespecified outcomes; groups similar at baseline regarding demographics and other important clinical characteristics; similar or absent co-interventions; adequate compliance with the interventions; and similar timing of primary outcomes for the intervention and control groups. The score of 1 was given if the domain fulfilled the Cochrane recommendations and 0 if not. Hence, the total score had a possible range from 12 (highest level of quality) to 0 (lowest level of quality). Two pairs of raters evaluated the studies. Each rater conducted independent evaluations, and agreement between raters in each pair was provided. When in doubt, the domain was scored as 0. A consensus-based total score was subsequently elaborated. A data extraction sheet was elaborated capturing the type of randomization, number of involved study centers, sample size and age of the participants, as well as outcome measures.

DATA ANALYSIS AND STATISTICS

The data were summarized descriptively, and agreement between researchers was assessed by Pearson's correlation coefficient (r). The frequency of described dimensions and categories of service provision according to ICSO-R (15), with the predefined selection of descriptors suggested by Røe et al. (26), are reported. Service provision was categorized regarding Location (i.e., country), Organization (public or private), Context (hospital or community), Facility (rehabilitation or general medical) and Profit orientation (yes/no). The Funding dimension was assessed according to public, private or insurance-based sources of money. For the Delivery dimension Strategy of the intervention (diagnostic/therapeutic/management/prevention), Target group (TBI specific or not), Service goals (improvement of body function/activities and participation/adaptation to environmental factors), Team

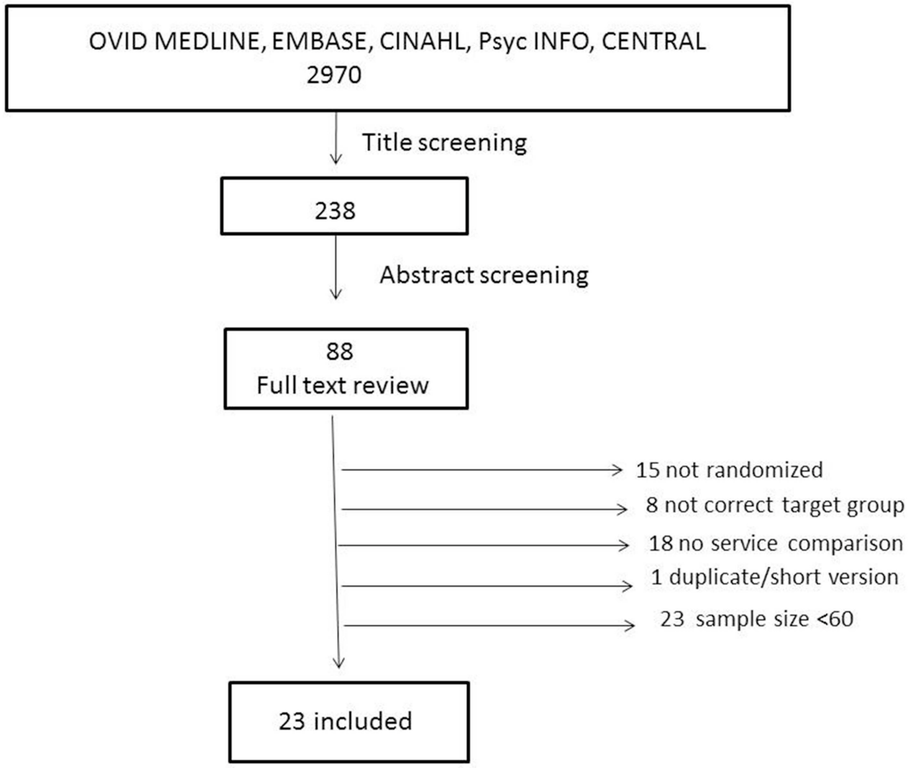

FIGURE 1 | Flow chart of inclusion process.

structure (interdisciplinary/multidisciplinary/single disciplines) and Mode of production, categorized as inpatient or outpatient delivery (inpatient or not), were assessed. We also attempted to disentangle whether these dimensions and categories varied between the intervention arms in the studies and summarized the main dimension/category differences. For the categories of Intensity, Aspects of time and Other, we could not apply the predefined terms from Røe et al. (26) we did not find applicable equivalents and used the descriptive approach by Kiekens et al. (17). Main outcome measurements from the selected studies are reported, along with the dimensions of the International Classification of Functioning, Disability and Health (ICF) (Body function, Activity and Participation, Environmental factors).

RESULTS

Descriptions of Studies

A parallel group design was applied in 22 of the included studies. The studies were usually conducted within a single center ($n = 20$), and none of the studies included more than 3 sites. The median sample size was 120, ranging from 60 to 1,156 included subjects, with 4,644 participants altogether. The mean age was 39 years old in both the intervention and control groups, with the mean age ranging from 24 to 57 years old in the individual studies. Studies targeted the effects of different contents and intensities of rehabilitation across physical, emotional, cognitive and vocational strategies, as well as comparing rehabilitation with waiting list and in- and outpatient services (**Tables 1**, **2**). In some of the studies, there was overlap between either participants or interventions. The studies by Winter et al. (39) and Moriarty et al. (40) represented the same intervention, focusing on the effects on the patients and their families, respectively. In the two studies by Bell et al., the intervention was conducted in a single center (28) and subsequently evaluated in a multicenter study (29) The studies by Wade et al. illustrated a replicated intervention (47, 48).

Quality of Studies

The quality of the studies was rated 7.00 (SD 2.11) and 6.61 (SD 2.02) by the two raters, with a high correlation between the raters ($r = 0.94$). At the single item level, the assessors had different scores on 5.43% (15) of the items, (concealment 3, co-intervention 8, compliance 4). See **Appendix 2** for the consensus based quality ratings for each study and items. The most common cause of a reduced quality score was lack of blinding, with only one study designed to allow for blinding of patients and none obtaining blinding of care providers. In addition, concealment of group allocation was poorly described in some of the studies, and the evaluation of absent or similar co-interventions across intervention arms was challenging.

TABLE 1 | Studies with differences between the intervention arms within the "Provider" dimension. Main outcomes as reported by the authors and the ICF dimensions covered.

Included studies	Content intervention	Content control	Main outcome (ICF dimensions covered by all outcome measures)
DIFFERENCES IN RESOURCES AND CONTEXT			
*Bedard et al. (27)	10 weeks of mindfulness- based cognitive therapy	Waiting list	*Symptoms of depression using the Beck Depression Inventory-II* (Body function)
*Bell et al. (28)	Telephone-based motivational interview post-discharge	Standard follow-up groups	*Composite outcome* (FIM, DRS, CIQ, FSE,GOS-E, EuroQol, NFI, PQOL, SF-36 and BSI) (Body function, Activities and Participation)
Bell et al. (29)	Scheduled telephone intervention	Treatment as usual	*Composite outcome* (FIM, DRS, GOS-E, Part-O) (Body function, activities and participation)
Berry et al. (30)	Individualized problem- solving intervention provided to family caregivers	Education-only control group	Caregivers: *Social Problem Solving Inventory-Revised, the Center for Epidemiological Studies-Depression scale the Satisfaction with Life scale, and a measure of health complaints* Patients: *Hamilton Depression Scale* (Body function)
*Bombardier et al. (31)	7 scheduled telephone calls, information, problem solving behavioral activation sessions over 9 months	Treatment as usual	*Brief Symptom Inventory-Depression (BSI-D) subscale, Neurobehavioral Functioning Inventory-Depression subscale, and Mental Health Index-5* (Body function)
Brenner et al. (32)	Health and wellness therapy	Waiting list	*Health Promoting Lifestyle Profile-II* (Activities and Participation)
*Cicerone et al. (33)	Intensive cognitive rehabilitation (15 h/w over 16 w)	Standard neurorehabilitation with individual, discipline-specific therapies	*Community Integration Questionnaire (CIQ) and Perceived Quality of Life scale (PQOL)* (Activities and Participation)
Heskestad et al. (34)	Cognitive-oriented consultation two weeks after the injury	No intervention	*Main outcome not stated but Postconcussion symptoms, Beck Depression Inventory, Epworth Sleepiness scale, Fatigue Severity Scale and SF-36 reported* (Body function, Activities and Participation)
Hoffman et al. (35)	Structured aerobic exercise regimen for 10 weeks	No treatment	*Beck Depression Inventory* (Body function)
McMillan et al. (36)	Group 1. Attention control training for 5 sessions over 4 weeks Group 2. Exercises	Control	*Self-report measures of cognitive function, mood or symptom reporting* (Body function, Activities and Participation)
*Ponsford et al. (37)	Group 1. Adapted cognitive behavioral therapy (CBT) Group 2. Non-individualized CBT	Waiting list	*Hospital Anxiety and Depression Scale (anxiety subscale), Depression, Anxiety and Stress Scale (depression subscale)* (Body function, Activities and Participation)
Sander et al. (38)	Brief intervention for modifying alcohol expectancies	Standard care	*Alcohol Expectancy Questionnaire-III Global Positive Expectancies and Cognitive and Physical Impairment scales; Readiness to Change Questionnaire; problem alcohol use* (Activities and Participation)
*Winter et al. (39) *Moriarty et al. (40)	Community re-integration focused on home based rehabilitation with home visits	Standard outpatient clinical care	*Target outcomes reflecting veterans' self- identified problems and self-rated functional competence (W) Family member depressive symptomatology, caregiver burden, caregiver satisfaction, acceptability of the intervention (M)* (Body function, Activities, Participation, Environmental factors)

**Indicates a statistically significant difference between the intervention arms in one or more of the study outcomes.*

Targeted Meso-Level Aspects of Services

The studies emerged from five different countries. A total of 14 of the studies were from the US, followed by 6 from the UK and one from each of the countries Canada, Australia and Norway. The organization was defined as public in 3 of the studies and not clearly stated in the remainder.

In one of the studies, the context was not possible to identify for the control group. In 70% of the studies, one or more of the interventions were conducted in hospitals, and in 30% of the studies, the interventions were conducted in the communities. In the studies conducted in hospital setting one or more of the intervention arms were performed in rehabilitation units and only one study included interventions confined only to a general hospital unit. None of the studies were conducted in nursing homes. In general, the studies provided no explicit information about the profit orientation

TABLE 2 | Studies with differences between the intervention arms in the Delivery dimension. Main outcomes as reported by the authors and the ICF dimensions covered.

Included studies	Content intervention	Content control	Main outcome (ICF dimensions covered by the outcome measures)
DIFFERENCES IN TEAM STRUCTURE			
*Rath et al. (41)	Problem solving-focused group treatment	Conventional neuropsychological rehabilitation	*Not stated but Cognitive skills, Psychosocial function and Problem solving assessed* (Body function, Activities and Participation)
DIFFERENCES IN MODE OF PRODUCTION			
Bowen et al. (42)	Pre-discharge Interdisciplinary rehabilitation	1. Post-discharge interdisciplinary rehabilitation 2. Outpatient treatment as usual	*The Wimbledon Self-Reported Scale of Emotions, Katz Adjustment Scale for Social Behavior, Cognition (Logical Memory and Wechsler Memory Scale Revised)* (Body function, Activities and Participation)
Salazar et al. (43)	Intensive, 8-week, in-hospital cognitive rehabilitation program	Home rehabilitation program with weekly telephone support	*Return to gainful employment and fitness for military duty* (Activities and participation)
*Vanderploeg et al. (44)	Cognitive didacticism with integrated interdisciplinary inpatient rehabilitation	Functional-experiential with integrated interdisciplinary rehabilitation	*Functional independence in living and return to work and/or school* (Activities and participation)
DIFFERENCES IN INTENSITY			
*Powell et al. (45)	Outreach treatment for two sessions per week for a mean of 27 weeks in a community settings	*Information with one home visit*	*Barthel index, the Brain Injury Community Rehabilitation Outcome-39* (Activities and Participation)
Slade et al. (46)	67% increase in intensity of inpatient therapy	Usual inpatient therapy	*Length of hospital stay*
DIFFERENCES IN ASPECTS OF TIME			
Wade et al. (47) *Wade et al. (48)	Early intervention (telephone or face-to-face counseling)	Usual follow-up	*Rivermead head injury follow-up questionnaire (97 + 98), Rivermead Postconcussion Symptoms Questionnaire (97)* (Body Functions, Activities, and Participation)
DIFFERENCES IN PEER INVOLVEMENT			
*Hanks et al. (49)	Mentor treatment after discharge	Treatment as usual	*Peer mentoring questionnaire; brief Symptom inventory-18, family assessment* *Device, Coping Inventory for Stressful Situations; Short Michigan Alcohol Screening Test, Medical Outcomes Study 12- Item Short-Form Health Survey, Community Integration Measure* (Body function, Activities and Participation, Environmental Factors)

**Indicates a statistically significant difference between the intervention arms in one or more of the study outcomes.*

of the services. In line with this finding, the funding dimension was impossible to determine in all except for one study (42).

Within the delivery dimension, statements specifically addressing service delivery according to the categories in ICSO-R were lacking. However, based on the information in the studies we found that 74% of the studies included a therapeutic strategy for the interventions, 17% were primarily managing, and 9% preventing in nature. In total 78% of the studies included improvement in body function as a service goal, and one third of the studies included multiple goals for the services. Only 22% of the studies included environmental factors as a goal for the interventions. In 4% of the active interventions and 52% of the control interventions, the team structure providing the services was difficult to disentangle. Only 13% of the active, interventions and 8% of the control interventions were deemed to be interdisciplinary, whereas 39% of the active and 17% of control interventions were multidisciplinary interventions. In more than 85% of the studies, the services were outpatient based.

Outcomes

The outcome areas covered were physical, cognitive and mental, and neuropsychological assessment of cognitive functions, as well as activity, and participation components and composite scores covering global functioning were also applied (**Tables 1**, **2**). Although, a wide variety of outcome measurements were applied with sparse overlap between studies all studies except Slade et al. (46) included functional outcome covering one or more of the ICF dimensions. The environmental factor was covered generally only through caregiver burden outcomes. In addition to the ICF dimensions, well-being and satisfaction, as well as quality of life, were addressed in the outcomes. In total, 12 studies reported statistically significant differences between the intervention and control groups in one or more of the outcomes (**Tables 1**, **2**). All studies addressed symptom burden or functional problems.

Intervention arm Contrasts Regarding Rehabilitation Services

Within the Provider dimension we did not find any studies in which Location, Organization (Public/Private) or Profit orientation varied between the intervention arms. In 14 of the studies we identified differences regarding Context and Resources (**Table 1**). These studies typically compared interventions with a waiting list or "treatment as usual" condition. Usually both Context and Resources varied between the intervention arms. The main impression is that additional rehabilitation Resources, as well as Context, influenced the outcomes in these studies, with reported effects on one or more of the outcomes in 7 of the studies. Human resources varied between the interventions in most of the studies (**Table 1**). In several of the studies, there were additional differences in Delivery aspects as well.

We choose to define Mode of production as the main Service difference among the interventions in the study by Bowen et al. (42), but context differences also existed between the intervention arms. Total of 9 studies were classified with the main differences between the intervention arms in the categories of the Delivery dimension and with variations in Team structure, Aspects of time, Intensity and Peer involvement (**Table 2**). The Team structure variations were related to the group or more individually based service delivery (41). As expected, Target groups were kept constant across the intervention arms. Strategy was also unchanged across all of the intervention arms. In five of the studies, statistically significant outcome differences between the intervention arms were identified (**Table 2**).

DISCUSSION

The present review provides an overview of randomized, rehabilitation trials with service provision relevance in the post-acute phase after moderate and severe TBI. Half of the studies reported statistically significant differences between interventions in one or more of the outcome measurements. That most of the studies focused on the rehabilitation strategy i.e., content, with implicit, more than explicit, variations in the service provision and delivery, was a challenge. Furthermore, the lack of universal terminology and reporting standards for the service aspects, as well as the diversity of interventions and outcome measures, prohibited analysis of the effects of service provision across studies, as well as metaanalytic approaches.

Rehabilitation service provision is complex and varies across health care settings and countries, with a lack of synthesized information regarding effective organization of services based on randomized trials (50). Successful outcomes at the patient level are dependent on the organization, capacity and quality of rehabilitation services at the macro-, meso- and micro-levels (51). Several reviews have been conducted regarding the effects of different interventions and treatment modalities targeting physical, cognitive and emotional problems after TBI (8, 52–59). However, very few evaluated directly the effects of differences in service provision and delivery supporting the gap in knowledge regarding post-acute services for TBI at the meso-level. Service provision and delivery related factors may thus influence outcome across reported significance. The review also illustrated that, when applying a structured framework, differences in service provision and delivery could be deduced from intervention studies, primarily evaluating programs at the micro-level.

The implicit components of services included in the treatment and interventions compared in clinical studies are an enormous challenge regarding the evaluation of effective service models. Thus, synthesizing evidence regarding effective components in service provision is also difficult. ICSO-R provided a tool for systematizing important elements of services across intervention arms. Describing the studies according to ICSO-R did, however, indicate that important elements of services varied across intervention arms and could influence the outcomes. One might argue that the majority of the studies were conducted before the ICSO-R was published. However, the aspects of services addressed in the ICSO-R have been relevant to service provision for decades (7). Laver et al. (14) conducted a systematic review regarding evidence for organizing health care for people with acquired brain injury, identifying 8 studies of TBI. When excluding studies with mainly mild TBI and those conducted in the acute phase, the studies included in Lavers' review overlapped with the present review. However, a main limitation is the current lack of subcategories in the ICSO-R, overlapping categories, and a lack of definitions. We applied some predefined subcategories suggested by Røe et al. (26). These predefined categories clearly failed to capture the main differences between studies regarding the intensity and timing of the intervention, as well as regarding team structure. These subcategories were developed to reduce overlap between categories, which is inherent to the original ICSO-R. This adjustment might have biased our results with over reporting of context differences and underreporting of organizational and facility differences. The new version of the ICSO-R that is being elaborated might provide a better tool for analyzing the effects of service provision in the future. The present review also illustrated that improving aspects of better information regarding service provision and delivery could be gained from the existing literature.

We categorized the studies according to the main service dimension and categories differing between the intervention arms (**Tables 1**, **2**). Based on this approach, we identified aspects of service provision and delivery that clearly could impact evaluations of the effects in these studies. Very few studies clearly stated whether the services were private or publicly organized. These aspects could impact patient selection beyond the socio-demographic characteristics reported in the studies. We did not identify any studies focusing on the funding dimension, although both public and private organization of services and type of funding are very important aspects for policy makers and stakeholders (60). Patients' payments and refunding of the services influence outcomes, but they were poorly described in the included studies. Future studies should address this aspect more directly because resources constitute a barrier to the implementation of services (61).

Neither the dimensions nor the categories in the ICSO-R are mutually independent. In the studies comparing specified interventions with waiting lists or usual care treatment (**Table 1**), the differences in the service provider dimension were evident, often with different contexts and more resources in the active interventions, compared to treatment as usual care and waiting lists. However, covariance with delivery aspects was inevitable in these studies. Some of the studies included in the present review rather explicitly targeted the mode of production (51–54), but comparing in- and outpatient services generally also implies differences in provision, i.e., context and facilities.

Covariance among categories within each dimension of the ICSO-R was even more evident. For example, in Bowen et al. (42), the mode of production with pre- and post-discharge comparisons of rehabilitation interventions co-varied with differences in the timing category (**Table 2**). In the studies with several intervention arms, the nature of differences could vary between the intervention arms, rendering the classification challenging. In the study by Bowen et al. (42), two of the intervention arms varied regarding the mode of production, whereas the third arm (treatment as usual) could be evaluated as having different service provision aspects (Context and Resources).

The ICSO-R was specifically developed to cover rehabilitation services at the meso-level (15). The primary goal of the majority of included studies in this review focused on the content of the interventions, i.e., the micro-level of services (5). The distinction between service delivery at the meso-level and content at the micro-level might not always be clear cut (22). Several of the studies identified in our literature search evaluated the effects of different neuropsychological approaches. Since intensity is a category in the ICSO-R, studies with slightly different intensities of rehabilitation were included, although intensity could be evaluated as an important aspect of the content. Difficulties in clear-cut distinctions between the meso- and micro-levels of services are accompanied by a lack of invariance across such aspects. Content of treatment is not included in the ICSO-R but is needed to assess the effects of rehabilitation. To address the effects of different service provision components on outcomes, a more specified, detailed and universally applied system for service provision and delivery is needed. To some extent, the needed process could be compared with the development of ICF (18). Hence, 17 years after the launching of ICF, its application as a framework for systematizing outcome evaluation is increasing (62). A revised version of the ICSO-R represents one step toward this goal. However, a universal and not too complicated taxonomy for the content of effective ingredients is also urgently needed (63).

Consequently, the effects of differences in rehabilitation services cannot be directly determined from the present review. Nevertheless, it is reasonable to assume that resources and contextual factors did contribute to the documented differences between the intervention arms. It was an important aspect of the aim to evaluate in-hospital vs. at-home services in several of the studies, i.e., differences in mode of production and context (42, 43). These studies failed to document major differences in outcomes, except for better patient satisfaction with at-home services (**Table 2**). This finding is in contrast to the experience of patients with stroke, in whom early supported discharge showed superior efficacy over in-hospital services (64). This difference might be caused by greater variability in the needs and goals of patients with TBI and also methodological limitations in the studies included in the present review. In contrast, Winter et al. and Moriarty et al. (25) documented improvements in individually targeted outcomes for patients, as well as their relatives in people centered in home care, compared to "treatment as usual." However, in these studies, the intensity/amount of rehabilitation could also have been different and impacted the outcome (**Table 2**). Variable influence in outcomes was indicated by variations in team structure, intensity and aspects of time, while Hanks et al. (49) study supported improved outcomes by peer involvement in the interventions.

The present review also underpins that replication of interventions across service providers, and delivery aspects might be important. The study by Bell et al. (28) indicated positive results of a telephone follow-up in a single center study, but it was not replicated with a multicenter design (29). Underpinning the need for validation studies, Wade et al. (48) documented significant results in their replicated study with early intervention (aspects of time). All, except one of the included studies targeted symptoms or functional problems as outcome. Increased use of common data elements and linking approaches between measurements may facilitate better comparison between studies in the future (65, 66).

The quality of the included studies varied, and reaching a maximum score might not be possible due to the lack of possibility of blinding patients and rehabilitation providers. We applied the CONSORT guidelines and scored the quality according to Furlan et al. (25) Rehabilitation might require an adapted scoring system acknowledging the special challenges in this field (67). For example, although not blinded to the intervention itself, blinding to its aims and mechanisms could be the best possible choice and could be acknowledged. The quality evaluation clearly revealed that improvement is needed in describing the concealment of randomization. Possibly more important for the results and their interpretation are better assessment and description of co-interventions. To evaluate the components related to the differences and effects in randomized rehabilitation trials, improved description of the provision and delivery of the services, along with the content of the interventions, is needed and should be included in quality evaluation systems.

The main limitations of the present review are the lack of inclusion and exclusion criteria for the ICSO-R categories and the lack of common descriptors of the services in the studies. This is an obstacle for the inclusion process of studies as well as for analyzing and reporting the influence on outcome in the studies.

CONCLUSION AND CLINICAL RELEVANCE

A lack of uniformity of data and collection methods, the heterogeneity of structures and processes of rehabilitation services, and the lack of common outcome measurements made the study results less generalizable and the comparison between studies difficult. Standardized descriptions of services, including provider, funding and delivery dimensions, could improve the service relevance of rehabilitation studies and give valuable information to many different stakeholders. A shorter version of ICSO-R with value sets may be needed for inclusion in rehabilitation studies description.

AUTHOR CONTRIBUTIONS

CR, CT, EH, OT, PA, and NA contributed to the theoretical background, framework for analysis and writing process. CR, CT, and EH conducted the data analysis and, together with NA, elaborated the first manuscript draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00557/full#supplementary-material

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