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Depression and cognitive sequelae after a traumatic brain lesion

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ABSTRACT

INTRODUCTION. To improve rehabilitation in young people with an acquired brain injury, the Danish Ministry of Health initiated the "National study on young brain injury survivors" in 2012. Using data from this initiative, we examined the changes in depression, cognition, global functional outcome and return to work/school among young traumatic brain injury (TBI) survivors.

METHOD. This was an observational one-year follow-up study based on data from "Danish registry for young adults with acquired brain injury". The main measures were Major Depression Inventory, neuropsychological examination, and Glasgow Outcome Scale - extended (GOS-E).

RESULTS. A total of 76 young TBI survivors attended two interdisciplinary examinations and had complete data. Sixty-six (86.8%) had rehabilitation between the two visits, and the global functional outcome was vastly higher at the second visit ($z = -3.373$, $p = 0.0007$). At the first versus the second visit, the prevalence proportion of depression was 14.5% (95% confidence interval (CI): 7.5-24.4) versus 10.5% (95% CI: 4.7-19.7), and for cognitive sequelae it was 31.6% (95% CI: 21.4-43.3) versus 19.7% (95% CI: 11.5-30.5). Patients with depression and/or cognitive sequelae had a lower GOS-E score ($p = 0.0016$) than patients without depression/cognitive sequelae and a negative association was found between depression, cognitive sequelae and return to work/school ($p = 0.045$).

CONCLUSION. Emotional and cognitive rehabilitation for young TBI survivors seems essential as depression and cognitive sequelae are associated with a lower global functional outcome and return to work/school.

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In 2012, the Danish Ministry of Health initiated "National study on young brain injury survivors" to ensure that young survivors of acquired brain injury (ABI) received sufficient and timely rehabilitation after their ABI. Accordingly, five regional outpatient clinics providing interdisciplinary evaluation of rehabilitation needs after discharge were established. Furthermore, the "Danish registry for young adults with acquired brain injury" (Danish acronym DRUE) [1] was created to gather systematic national data on the functional outcome among young Danish ABI survivors (15-30 years).

A cross-sectional study based on DRUE data determined that young survivors of traumatic brain injury (TBI) examined less than a year after injury had a higher prevalence of depression than the general population and that patients with both depression and cognitive sequelae had a significantly lower global functional outcome than patients without depression and cognitive sequelae [2]. However, to the best of the authors' knowledge, follow-up studies among adolescents and young adults with moderate to severe TBI are very sparse [3] but seems much needed, as adolescence and young adulthood are life periods with many transitions in relation to independency, peer relations and education.

Accordingly, we present a registry-based observational one-year follow-up study with the main aims of determining the changes in depression, cognitive sequelae and global functional outcome from the first visit (less than a year after the insult) to the subsequent one-year follow-up, and to investigate whether depression and cognitive sequelae were associated with global functional outcome and return to work/school (RTW).

METHOD

Design

This was an observational follow-up study based on data from the national clinical registry DRUE [1]. DRUE contains information about young survivors of TBI referred in the period from October 2013 to December 2016 to one of the five outpatient clinics that were established in the five Danish health regions as part of the national health initiative. The patients were offered two interdisciplinary examinations: one after referral and one at a one-year follow-up.

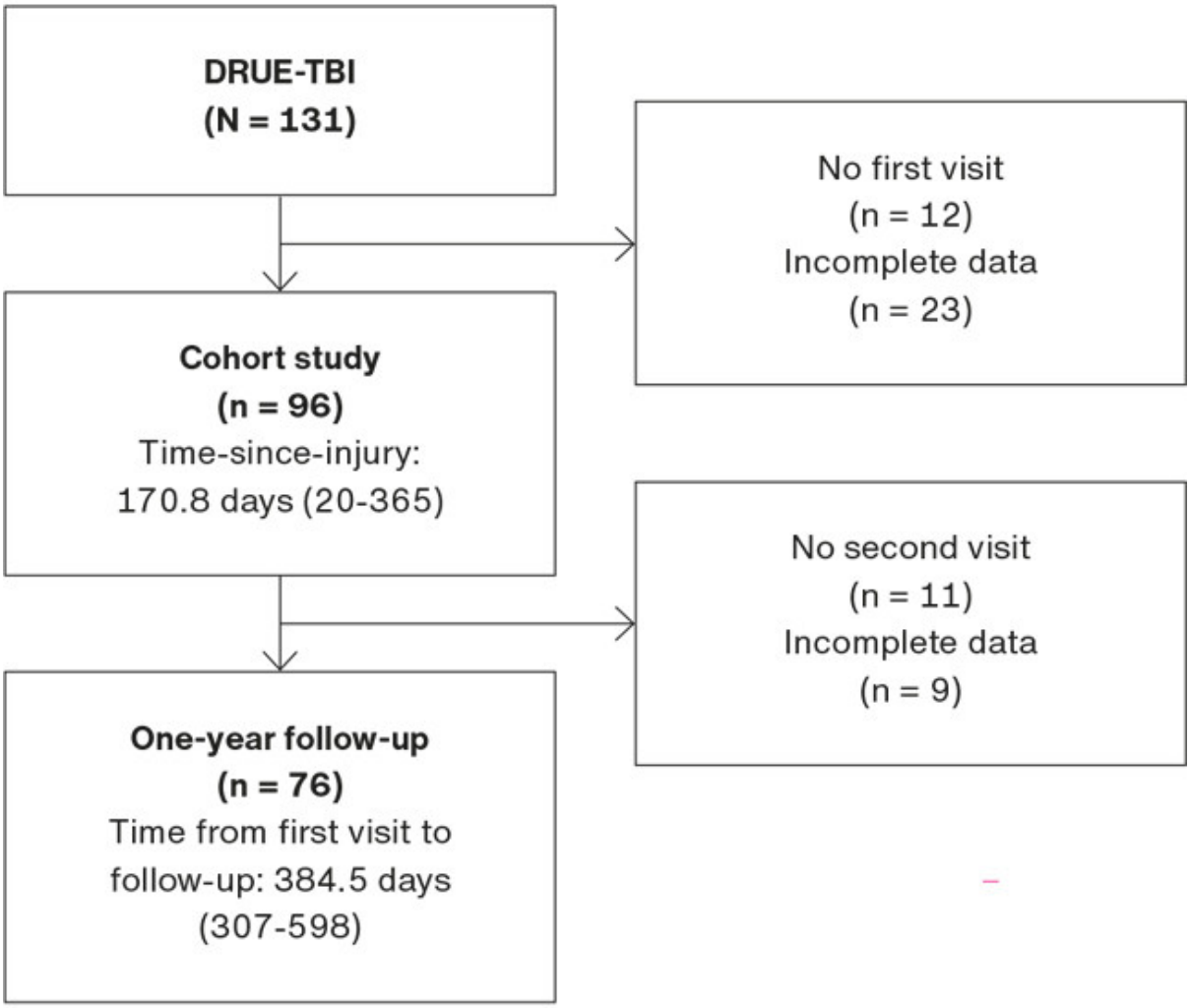
The study is approved by The Danish Clinical Registries (DRUE ref. no. 4) and registered with the North Denmark Region (ref. no. 2018-15).

Population

This study is based on the DRUE-TBI population (n = 131), which consists of adolescents and young adults registered in DRUE with a diagnostic code denoting a traumatic intracranial brain lesion (ICD-10 diagnostic codes S.06.1-S.06.9) [4] who were invited to the first interdisciplinary examination less than a year after their injury. The participants were 15-30 years old at the time of referral (cf. https://www2.ugeskriftet.dk/files/a02220108_-_supplementary.pdf).

Patients from the DRUE-TBI population were included in this study if they had complete data on the Major Depression Inventory (MDI), eight neuropsychological tests and the Glasgow Outcome Scale – Extended (GOS-E) (cf. Measurements and supplementary materials) at both the first visit and at the one-year follow-up (cf. **Figure 1**).

FIGURE 1 Flow chart of the included and excluded patients.



DRUE = Danish registry for young adults with acquired brain injury; TBI = traumatic brain injury.

Measurements

The following data were extracted from DRUE: demographic data, information about rehabilitation before the first visit, rehabilitation between the two interdisciplinary examinations, employment status, absence from job/school due to illness [5-7], the MDI [8], eight neuropsychological tests [9-12] and the GOS-E [13] (please see Box 2 in the supplementary materials for further description). Cognitive sequelae were defined as performance scores that were ≥ 2 standard deviations (SD) below the norms [10, 14] or non-completion due to cognitive difficulties of at least two subtests [2].

Statistical analysis

A descriptive analysis of the differences between the included and excluded patients was conducted.

The prevalence proportions of depression and cognitive sequelae as well as rehabilitation between the first visit

and the follow-up were calculated with 95% confidence intervals (CI).

The Wilcoxon signed-rank test was used to examine whether GOS-E had changed from the first to the second visit and Fisher's exact test was used to examine whether the change in GOS-E was associated with time-since-injury. For that analysis, two ranges of "time-since-injury" (time from injury to the first visit) were used: 1) < 180 days and 2) ≥ 180 days, to investigate whether an early first examination (less than six months after the injury) was associated with a GOS-E change. Furthermore, the two-sample Wilcoxon rank-sum test was used to examine whether the GOS-E score differed between the two patient groups 1) patients with depression and/or cognitive sequelae and 2) patients who had neither depression nor cognitive sequelae. Finally, the χ^2 test was used to examine whether an association existed between depression, cognitive sequelae and RTW.

All analyses used a two-tailed significance level of $p < 0.05$. Data were analysed using Stata, version 16.0 [15].

Data availability statement

The data that support the findings of this study are available from the Danish Clinical Registries. Restrictions apply to the availability of these data, which were used under license for this study. Data requests for research purposes may be made by application to the Danish Clinical Registries via their home page or by e-mail.

Trial registration: not relevant.

RESULTS

A total of 76 young TBI survivors were identified as having complete data at both visits. Among the 76 included patients, 54 (71.1%) were males and the median age at the second visit was 23.9 years (range: 16.4-33.3 years). Characteristics of the included and excluded patients are presented in **Table 1**.

TABLE 1 Descriptive data for included and excluded patients.

	Included	Excluded	
	complete data (n = 76)	incomplete data, 2nd visit (n = 9)	no 2nd visit (n = 11)
Males, n (%)	54 (71.1)	7 (77.8)	10 (90.9)
Age at injury (range), yrs	22.3 (15.0-30.6)	21.8 (16.4-26.3)	26.5 (16.3-30.6)
Age at 1st visit (range), yrs	22.8 (15.3-31.0)	22.2 (17.4-26.7)	26.8 (16.4-31.0)
Age at 2nd visit (range), yrs	23.9 (16.4-32.3)	23.1 (18.4-27.8)	
Time from injury to 1st visit (range), days	160.5 (20-362)	144 (37-365)	141 (33-282)
Time from 1st to 2nd visit (range), days	384.5 (307-598)	378 (319-427)	
Rehabilitation before 1st visit, n (%)	44 (58)	6 (67)	< 3
GOS-E score at 1st visit (± SD)	5.6 (± 1.3)	5.8 (± 1.1)	6 (± 1.5)
Depression at 1st visit, n (%)	11 (14.5)	< 3	< 3
Cognitive sequelae at 1st visit, n (%)	24 (31.6)	4 (44.4)	5 (45.5)

GOS-E = Glasgow Outcome Scale – Extended (scale 1-8); SD = standard deviation.

Prevalence proportion of depression and cognitive sequelae

The prevalence proportion of depression was 14.5% (95% CI: 7.5-24.4) at the first visit and 10.5% (95% CI: 4.7-19.7) at the follow-up. Seven of the eleven patients who met the diagnostic criteria for depression at their first visit were in remission at the follow-up, but four still met the diagnostic criteria and another four new cases were identified.

The prevalence proportion of cognitive sequelae was 31.6% (95% CI: 21.4-43.3) at the first visit and 19.7% (95% CI: 14.5-30.5) at the follow-up. Thus, 11 of the 24 patients who met the defined criteria for cognitive sequelae at the first visit did not meet the criteria at the follow-up. In contrast, two patients in the cohort had experienced a deterioration in their neuropsychological performances and subsequently met the definition of cognitive sequelae at their second visit. Among the 76 included patients, 43.4% (95% CI: 32.1-55.8) had at least one performance score ≥ 2 SD below the norm.

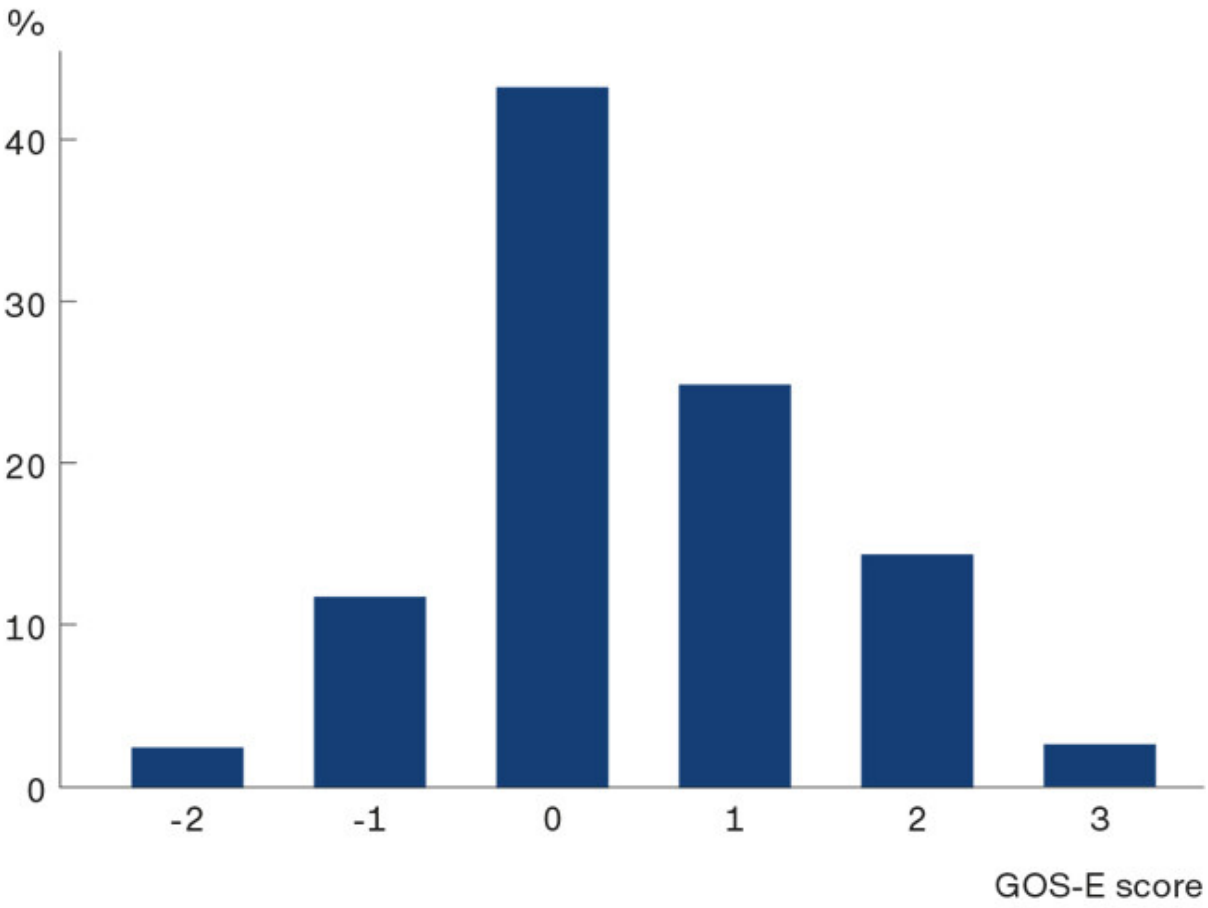
Rehabilitation between the first and second visit

A total of 66 (86.8%) of the included young TBI survivors reported that they participated in rehabilitation between the first and the second visit, with 55/66 (83.3%) participating in more than one type of rehabilitation. The primary rehabilitation initiatives focused on education and/or work skills (60.1%), physical functioning (57.9%) and activities of daily living (50%).

Global functional outcome

The GOS-E score was significantly higher at follow-up than at the first visit ($z = -3.373$, $p = 0.0007$). The distribution of the changes in the GOS-E score are shown in **Figure 2.** The positive change in the GOS-E score was not associated with the first examination being either before or after six months post-injury (Fisher's exact test = 0.738).

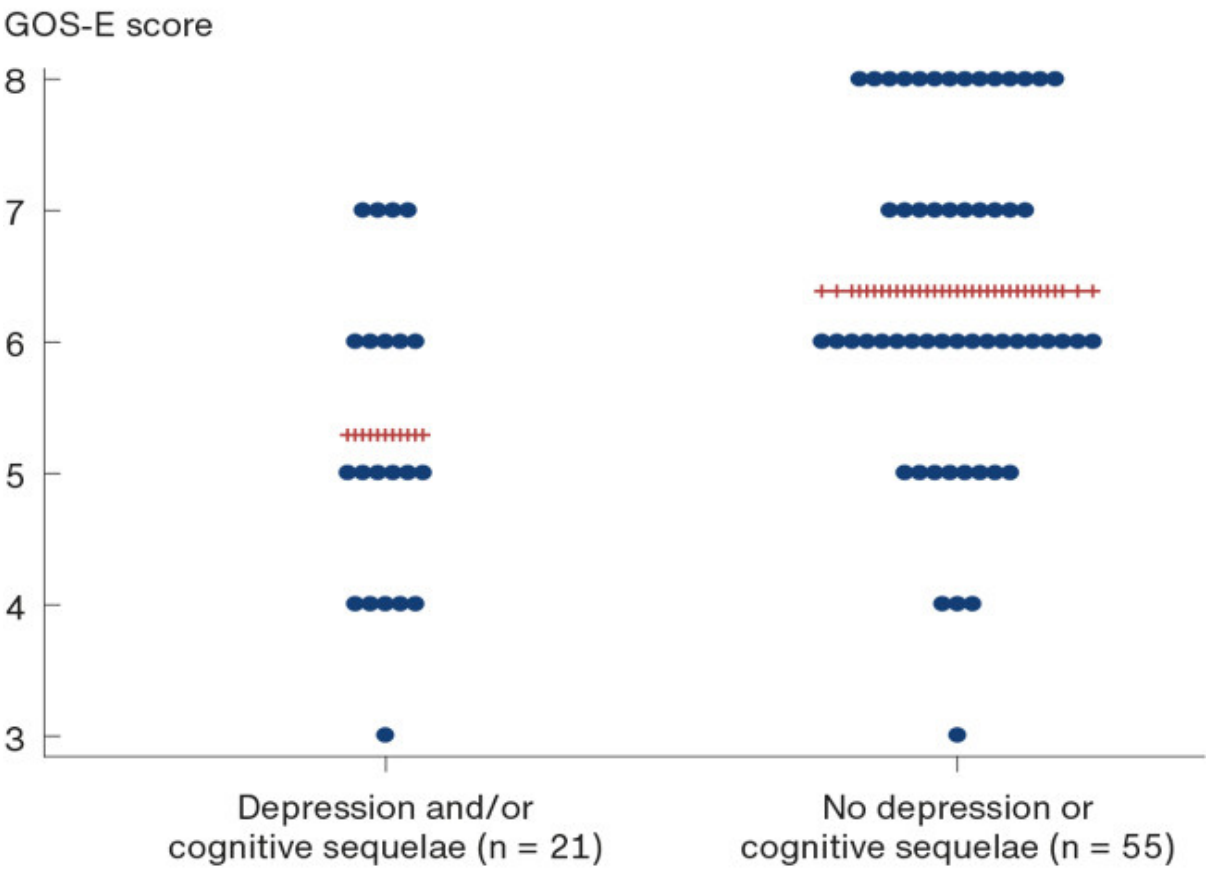
FIGURE 2 Distribution of change in the Glasgow Outcome Scale – Extended (GOS-E) score from the first visit (less than a year after the insult) to the subsequent one-year follow-up.



Association between depression, cognitive sequelae and global functional outcome

The mean GOS-E score at follow-up is presented in **Figure 3** for patients with depression and/or cognitive sequelae (n = 21) and for patients without depression and cognitive sequelae (n = 55). At the one-year follow-up visit, patients with depression and/or cognitive sequelae had a lower GOS-E score than patients without depression and cognitive sequelae (z = 3.160, p = 0.0016), and the absolute mean difference was 1.1 (95% CI: 0.5-1.7).

FIGURE 3 Distribution of the individual Glasgow Outcome Scale – Extended score at the one-year follow-up for 1) patients with depression and/or cognitive sequelae and 2) patients without depression and cognitive sequelae.



+) The mean for the two groups.

Association between depression, cognitive sequelae and return to work/school

Among the 76 included patients, 66 (86.8%) were enrolled in education or had a job before the TBI. Of these, 29 (43.9%) had RTW at the first visit, and a total of 39 (59.1%) had RTW at the follow-up visit. Additionally, a negative association was found between RTW at follow-up and depression and/or cognitive sequelae (Pearson χ^2 (1) = 4.0169, p = 0.045). Among the patients with depression and/or cognitive sequelae, 36% had RTW, whereas 65% of the patients without depression and cognitive sequelae had RTW.

DISCUSSION

This registry-based observational follow-up study found a substantial improvement in global functional outcome at the follow-up, but a stable prevalence proportion of depression and cognitive sequelae across the study period. The study also detected that patients identified with depression and/or cognitive sequelae had a

significantly poorer global functional outcome than other patients (Figure 3), and a negative association was found between the presence of depression and/or cognitive sequelae and RTW.

The stable prevalence proportion of depression from the first visit to follow-up is consistent with the existing literature on adults with moderate to severe TBI. Hart et al. reported a stable prevalence proportion of depression until two years after the injury [16], whereas Alway et al. found a stable prevalence proportion of mood disorder until five years after the injury [17]. However, a stable overall prevalence proportion could conceal individual-level variations [16], which resonates with our findings as both remission and development of symptoms were detected.

The stable prevalence proportion of cognitive sequelae seems to be consistent with the existing literature, as both improvement and deterioration of cognitive functioning have been detected up to five years after the injury [18, 19]. Additionally, the existing literature indicates that recovery of cognitive functioning varies across domains, with a slower recovery of more complex cognitive functioning [18]. The results of our study indicate that 20-40% of the adolescents and young adults with moderate to severe TBI have long-lasting cognitive sequelae, which most likely affect their ability to live an independent life and achieve an education [18].

Improvement in the global functional outcome was detected as 42.1% had a higher GOS-E score at follow-up than at their first visit, whereas only 14.5% experienced a deterioration (Figure 2). The substantial improvement from the first to the follow-up visit may be owed to several factors. Firstly, the detected improvement may be a result of the national health initiative "National study on young brain injury survivors", as almost nine out of ten included patients participated in rehabilitation initiated and financed by the patients' municipalities between the first visit and the follow-up. This may potentially indicate that continuous evaluation of rehabilitation needs and initiation of post-acute rehabilitation can improve outcome. Secondly, the improvement may potentially be associated with time-since-injury and consequently be a result of spontaneous recovery/plasticity. However, the statistical analysis showed that the improvement in GOS-E was not associated with time-since-injury, indicating that improvement was evident among both patients examined for the first time less than six months after their injury and among patients examined for the first time 6-12 months after their injury. Finally, improvement in global functional outcome beyond one year after the injury is also seen in prospective studies with follow-up more than two years after the injury [20]. However, this study indicates that global functional outcome is a dynamic factor. Hence, both improvement and deterioration in the global functional outcome were detected over time.

Furthermore, the fact that the adolescents and young adults with depression and/or cognitive sequelae had a consistently lower global functional outcome (Figure 3) and were less likely to have RTW at follow-up than other patients indicates that rehabilitation after TBI should focus on both cognitive and emotional sequelae and that some of the young survivors need ongoing emotional support and rehabilitation.

Study limitations

Although the study was based on data from a Danish clinical quality registry, the study sample only represents about one fifth of the total population of Danish adolescents and young adults who were expected to have a traumatic intracranial lesion in the study period. Furthermore, the fact that the study sample participated in a national health initiative, which included comprehensive interdisciplinary examination after discharge, evaluation of rehabilitation needs and collaboration with the patients' municipalities may affect the generalisability of the results.

Information about rehabilitation was based on the patients' and relatives' report and were categorised into eight categories in DRUE. The exact extent and nature of rehabilitation provided for individual patients during the follow-up period was not available in DRUE. Thus, the study cannot investigate whether the improvement in

global functional outcome was associated with the specific rehabilitation provided during the follow-up period.

The information about return to work or school does not include information about the length or stability of the work/school affiliation. Thus, the study cannot conclude whether the patients will complete their education or if they have a stable labour market attachment.

CONCLUSION

Nearly all youngsters with TBI who participated in the Danish DRUE initiative and were included in this study were offered publicly financed rehabilitation after their first interdisciplinary examination. At the follow-up, the cohort had improved considerably with respect to global functional outcome, but patients with depression and/or cognitive sequelae had a consistently lower global functional outcome than other patients, and a negative association was found between depression, cognitive sequelae and RTW. This indicates a need for an ongoing focus on the emotional and cognitive sequelae after TBI and on providing adequate rehabilitation to young TBI survivors.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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