Depression and cognitive sequelae among Danish adolescents and young adults (15-30 years old) with moderate to severe traumatic brain injury

Ryttersgaard, Trine Okkerstrøm

DOI (link to publication from Publisher):
10.54337/aau527272897

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

DEPRESSION AND COGNITIVE SEQUELAE AMONG DANISH ADOLESCENTS AND YOUNG ADULTS (15-30 YEARS OLD) WITH A MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

BY
TRINE OKKERSTRØM RYTTERSGAARD

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
DENMARK

DEPRESSION AND COGNITIVE SEQUELAE AMONG DANISH ADOLESCENTS AND YOUNG ADULTS (15-30 YEARS OLD) WITH A MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

by

Trine Okkerstrøm Ryttersgaard

AALBORG UNIVERSITY
DENMARK

Dissertation submitted

.

Dissertation submitted:	November 2022
PhD supervisor:	Carsten Reidies Bjarkam, Professor, MD, PhD, DMSc Department of Neurosurgery, Aalborg University Hospital
Assistant PhD supervisors:	Søren Paaske Johnsen Professor, MD, PhD, Danish Center for Clinical Health Services Research, Aalborg University Hospital
	Jens Østergaard Riis MSc in Psychology, Chief of Neuropsychology Department of Neurosurgery, Aalborg University Hospital
	Poul Henning Mogensen (until summer 2020) MD, PhD Department of Neurology, Aalborg University Hospital
PhD committee:	Clinical Professor Michael Lyhne Gaihede (chair) Aalborg University, Denmark
	Professor Randi Starrfelt University of Copenhagen, Denmark
	Professor Marianne Løvstad Sunnaas Rehabilitation Hospital / University of Oslo, Norway
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-912-7

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Stibo Complete, 2022

LIST OF PAPERS

The thesis is based on the following four papers:

1. Ryttersgaard TO, Johnsen SP, Riis JØ, Mogensen PH, Bjarkam CR. Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review. *Scandinavian Journal of Psychology*, 2020, 61(2), p. 297-306.

2. Ryttersgaard TO, Riis JØ, Johnsen SP, Mogensen PH, Bjarkam CR. Depression and cognitive sequelae registered within the first year among young Danish TBI survivors. *Scandinavian Journal of Psychology*, 2020, 61(5), p. 663-670.

3. Ryttersgaard TO, Riis JØ, Johnsen SP, Mogensen PH, Bjarkam CR. Depression and cognitive sequelae after a traumatic brain lesion. 2022. Accepted for publication in Danish Medical Journal.

4. Ryttersgaard TO, Valentin JB, Johnsen SP, Riis JØ, Bjarkam CR. Use of antidepressants among adolescents and young adults with traumatic brain injury. 2022. Submitted

ENGLISH SUMMARY

Moderate to severe traumatic brain injury (TBI) can result in physical, cognitive, emotional, and behavioural sequelae, and might have enormous consequences for the person injured as well as the family. Additionally, TBI do have socioeconomic consequences and is characterised as a global burden. Adolescents and young adults with moderate to severe TBI must participate in rehabilitation and adjust to a new functional level at the same time as they are about to have an education, get a job and live an independent life as well as they might have to live with TBI sequelae for many years. Taken together it seems evident to ensure that young TBI survivors have the best possibilities to achieve the best outcome and decrease the risk of secondary sequelae such as psychiatric illness and job-loss. To accommodate this the Danish Ministry of Health founded the national project 'National study on young brain injury survivors' in 2012, which resulted in the establishment of five regional outpatient clinics and the national clinical register 'Danish register for young adults with acquired brain injury' (Danish acronym: DRUE).

The aim of this thesis were to 1) review the existing knowledge on depression among adolescents and young adults with moderate to severe TBI, 2) determine the prevalence of depression and cognitive sequelae after TBI among adolescents and young adults registered in DRUE and examined less than a year after the injury), 3) determine the prevalence of depression and cognitive sequelae at the follow-up approximately one-year after the first visit, 4) investigate whether depression and cognitive sequelae are associated with outcome and return to school/work and to 5) investigate the use of antidepressants from 1-year pre-injury to 5 years post-injury.

The thesis is based on a systematic literature review, a cohort study, an observational one-year follow-up study and a matched cohort study with long-term follow-up. The systematic review is based on systematic literature searches in the PubMed database, Embase, PsychInfo and Cochrane. The cohort study and the one-year follow-up study are based on data from DRUE, and the matched cohort study is based on data from several nationwide population-based registries, which was linked by the unique civil personal register number.

In **Paper I** we confirmed that studies on depression after moderate to severe TBI among adolescents and young adults are sparse, as only seven studies were identified. The prevalence proportion varied from 1.3%-60%, and due to low methodological quality in many of the studies, an estimated prevalence proportion was not calculated. In **Paper II** we found that among Danish adolescents and young adults with an intracranial traumatic lesion examined less than a year after injury 14.6% (95% CI: 8.2-23.3) fulfilled the diagnostic criteria for depression and 34.4% (95% CI: 25.0-44.8) fulfilled the definition of cognitive sequelae. Additionally, we determined that young TBI survivors with depression and cognitive sequelae had a significantly lower

global functional outcome (z=3.987, p=0.0001) compared to young survivors without depression and cognitive sequelae. In **Paper III**, we found a stable prevalence proportion of depression and cognitive sequelae at the follow-up visit compared to the first visit. Furthermore, we determined that the global functional outcome had improved (z= -3.373, p=0.0007), but young survivors with depression and/or cognitive sequelae had a continuing lower global functional outcome (z=3.160, p=0.0016) and were in risk of not returning to school/work (Pearson chi2(1) = 4.0169, p=0.045). In **Paper IV** we found that Danish adolescents and young adults with an intracranial traumatic lesion had a consistently higher prevalence proportion of dispensed antidepressants from injury to 5 years post-injury compared to the matched general population.

In conclusion, the findings in this thesis indicate that young survivors of moderate to severe TBI are more vulnerable than their age-matched peers, as depression and cognitive sequelae are frequent among young TBI-survivors and as they have a continuously higher use of antidepressants compared to the general population. Furthermore, our results indicate that the young survivors with depression and/or cognitive sequelae have a lower global functional outcome and have difficulties with return to work/school, why it seems relevant to identify the young TBI-survivors in risk of prolonged sequelae.

DANSK RESUME

Moderat til svær traumatisk hjerneskade kan resultere i fysiske, kognitive, emotionelle og adfærdsmæssige vanskeligheder, som kan have store konsekvenser for den ramte og dennes familie. Derudover har traumatisk hjerneskade væsentlige socioøkonomiske konsekvenser og er blevet karakteriseret som en byrde for verdenssamfundet. Unge, som får en moderat til svær traumatisk hjerneskade, skal deltage i rehabilitering og tilpasse sig et nyt funktionsniveau samtidig med, at de skal vælge uddannelse, få et job og opnå selvstændig livsførelse. Derudover risikerer unge med traumatisk hjerneskade at skulle leve med de mulige følger i mange år. Derfor synes det essentielt at sikre at unge med traumatisk hjerneskade får de bedste muligheder for at opnå et så godt funktionsniveau som muligt samtidig med, at man mindsker risikoen for sekundære følger såsom psykisk lidelse og arbejdsløshed. For at imødekomme dette iværksatte Sundhedsministeriet i 2012 det nationale projekt "Styrket indsats for unge med erhvervet hjerneskade", hvilket resulterede i fem regionale ambulatorier og etablering af den kliniske kvalitetsdatabase 'Dansk register for unge med erhvervet hjerneskade' (DRUE).

Formålet med denne afhandling er at 1) gennemgå den eksisterende viden om depression hos unge med moderat til svær traumatisk hjerneskade, 2) fastlægge prævalensen af depression og kognitive vanskeligheder efter traumatisk hjerneskade blandt unge, som er registreret i DRUE og er undersøgt mindre end et år efter hovedtraumet, 3) fastlægge prævalensen af depression og kognitive vanskeligheder ved opfølgningen ca. 1 år efter det første besøg, 4) undersøge om depression og kognitive vanskeligheder er associeret med det overordnede funktionsniveau samt tilbagevenden til uddannelse/erhverv og at 5) undersøge forbruget af antidepressiv medicin fra 1 år før hovedtraumet og til fem år efter.

Afhandlingen er baseret på et systematisk litteraturreview, et kohortestudie, et etårs opfølgningsstudie og et matchet kohorte studie med langtidsopfølgning. Det systematiske litteraturreview er baseret på en systematisk litteratursøgning i PubMed databasen, Embase, PsychInfo og Cochrane. Kohortestudiet og etårs opfølgningsstudiet er baseret på data fra DRUE, og det matchede kohorte studie er baseret på data fra flere danske nationale registre, hvor data blev linket via det unikke CPR-nummer.

I **studie I** bekræftede vi, at der er få studier, som har undersøgt depression blandt unge med moderat til svær traumatisk hjerneskade, da kun syv studier blev identificeret. Prævalensen af depression varierede fra 1,3-60 % og flere af studierne var kendetegnet ved lav metodisk kvalitet, hvorfor en estimeret prævalens proportion ikke blev beregnet. I **studie II** fandt vi, at blandt danske unge med en traumatisk intrakraniel læsion som blev undersøgt mindre end et år efter skaden opfyldte 14,6 % (95 % CI: 8,2-22,3) de diagnostiske kriterier for depression, mens 34,4 % (95 % CI: 25,0-44,8)

opfyldte definitionen for kognitive følger. Derudover fandt vi, at de unge, som opfyldte kriterierne for depression og kognitive følger, havde et signifikant lavere globalt funktionsniveau end de unge, som ikke havde depression og kognitive følger (Z=3.987, p=0.0001). I **studie III**, fandt vi, at prævalensen af depression og kognitive følger var stabil mellem de to besøg, mens det globale funktionsniveau var blevet markant bedre (z=-3,373, p=0,0007). Imidlertid havde unge med depression og/eller kognitive følger et lavere globalt funktionsniveau (z=3,160, p=0,0016) og var i risiko for ikke at vende tilbage til uddannelse/arbejde (Pearson chi2(1)=4,0169, p=0,045). I **studie IV** fandt vi, at danske unge med en traumatisk intrakraniel læsion havde et vedvarende højere forbrug af antidepressiv medicin fra hovedtraumet til fem år efter sammenlignet med den matchede baggrundsbefolkning.

Sammenfattende antyder resultaterne i denne afhandling, at unge med moderat til svær traumatisk hjerneskade er mere sårbare end deres jævnaldrende. Dette hænger sammen med, at flere af dem må leve med depression og kognitive vanskeligheder efterfølgende, og at de har et højere forbrug af antidepressiv medicin i forhold til deres jævnaldrende. Derudover antyder vores resultater, at unge med depression og/eller kognitive følger har et lavere globalt funktionsniveau og har udfordringer med at vende tilbage til uddannelse/arbejde, hvorfor det synes relevant at identificere de unge som er i risiko for vedvarende følger.

ACKNOWLEDGEMENT

The work presented in this thesis was conducted from 2018 to 2022 during my employment at Department of Neurology, Aalborg University Hospital, but the journey started in 2014 when I became leader of the project 'National study on young brain injury survivors' in Denmark North Region. I had the pleasure to be part of the opening of the outpatient clinic 'Styrket indsats for unge med erhvervet hjerneskade' at Department of Neurology, Aalborg University Hospital, and the establishment of 'Danish register for young adults with acquired brain injury'.

My PhD journey has been four interesting, educational, and emotional years. I am very grateful that I got this unique possibility to become a skilled researcher and I want to express my gratitude to all the people who have assisted and encouraged me throughout the process.

I want to send a special thanks to the following persons:

My main supervisor Carsten Bjarkam Reidies. A very special thanks to you. You have showed me the way into research and encouraged me with your tremendous knowledge. Thank you for trusting me when I doubted in myself and for your continuous assistance as well as your flexibility when GDPR and Corona were obstacles on the way.

My co-supervisor and head of neuropsychology Jens Østergaard Riis. Firstly, a huge thanks for trusting me to be the leader of the project 'National study on young brain injury survivors' in Denmark North Region nine years ago. Thank you for your encouragement and tremendously knowledge on neuropsychology. You have been my mentor in neuropsychology for many years and it has been a pleasure to have had you by my side on this PhD journey.

My co-supervisor Søren Paaske Johnsen. A special thanks for showing me the way into epidemiology and for encouraging me with your tremendously knowledge. A huge thanks for your flexibility and innovation of my project when GDPR were an obstacle on the way – I would not have had a Paper IV without your help. Also a huge thanks for letting me be part of Danish Center for Clinical Health Services Research – it has been very educational for me.

My co-supervisor Poul Henning Mogensen. Thank you for your engagement in the project and for making it possible for me to talk about my research all over the world.

Maja Søndergaard Worm. Thank you for this journey. It has meant a lot for me that you have been their all the way and that we have had the possibility to discuss DRUE.

Senior statistician Jan Brink Valentin. Thank you for your patience and indescribable help with the statistics in Paper IV.

Department of Neurology, Aalborg University Hospital. Thank you for giving me this opportunity and for supporting me professional and financial all the way.

The national committee on 'Styrket indsats for unge med erhvervet hjerneskade' and DRUE. Thank you for the cooperation and for approving the use of data from DRUE.

My former colleagues at 'Styrket indsats for unge med erhvervet hjerneskade' at Aalborg University Hospital. I will always look back at the four years in the project with pride – we did a fantastic job, and I am grateful for your professional competence, commitment, and personal friendship.

The neuropsychologist at Department of Neurology, Aalborg University Hospital and Neuroenhed Nord. Thank you for your workplace relationship, your encouragement and for have listened to my frustrations over a cup of coffee.

My colleagues at 'Demensenheden' and Department of Neurology, Aalborg University Hospital. Thank you for letting me keep in touch with the clinical work while becoming a researcher. I am proud of being part of a department which is characterised by professional competence, community, and the best parties in town.

Department of Child and Adolescent Psychiatry. Thank you for educating me in depression among adolescents and letting me follow the examinations of some of your patients. A special thanks to Søren Martin Andersen and Mille Benfeldt Kjær who made my visits at the department possible.

Jette Frost Jepsen, Librarian at Aalborg University Hospital. Thank you for your tremendous help with the development of the systematic literature search in Paper I.

Kirstine Ahlmann Hjuler for your thorough language editing.

Lundbeck Foundation who supported my participation at the 3ed International conference on Paediatric acquired brain injury.

Finally, a heartfelt thanks to my family and friends: To my husband Paw who have supported and cheered on me not just in the last five years, but as long as we have known each other. To my two lovely sons Emil and Simon, whom with their unconditional love have filled me with courage and pride. To my mom and dad who always have believed in me and have been a tremendously help in our life, I am grateful for that. To the rest of my family and all my friends: Thank you for your encouragement, talks over a glass of wine and many hours of laughter. I am very grateful to have all of you in my life.

LIST OF ABBREVIATIONS

ABI: Acquired brain injury

ANOVA: Analysis of variance

BDI: Becks depression inventory

CI: Confidence interval

CPR: Civil personal register number

DCRS: The Danish civil registration system

DRS: Disability rating scale

DRUE: Danish register for young adults with acquired brain injury (Danish acronym)

DSM-IV: Diagnostic and statistical manual of mental disorders, 4th ed.

FIM: Functional independence measurement

GCS: Glasgow coma scale

GOS-E: Glasgow outcome scale – extended

GP: General practitioner

ICD-10: International statistical classification of diseases & related health problems, 10th rev.

MDI: Major depression inventory

NPR: The Danish national patient register

PFC: Prefrontal cortex

PHQ-9: Patient health questionnaire-9

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

PTA: Post traumatic amnesia

RoB: Risk of bias

RTW: Return to work/school

SADS-L: Schedule of affective disorder and schizophrenia-L

SD: Standard deviation

TAD: Test of anxiety and depression in childhood and adolescence

TBI: Traumatic brain injury

TMT-A: Trail making test A

TMT-B: Trail making test B

UK: The United Kingdom

US: The United States of America

WAIS-IV: Wechsler adult intelligence scale – Fourth edition

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

Traumatic brain injury (TBI) is recognised as a global health problem,[1,2] with severe personal and social consequences, which can result in major socioeconomic costs.[3,4] A TBI during adolescence or young adulthood may have even greater consequences, as the TBI affects a brain that is still maturing and it might influence an ongoing otherwise normal development.[5] Furthermore, adolescents and young adults suffering a TBI must live with sequelae for many years, and it might have a negative influence on their educational and professional career opportunities, as well as their possibility to live an independent life.

1.1. TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is an acquired brain injury where an external force causes a sudden disruption of normal brain function and/or brain structure.[6,7] The external force can be either a direct blow to the head or an indirect force causing damage to the brain such as acceleration/deceleration or blast-related forces.[7–9] Disruption of normal brain function includes loss or alteration of consciousness, posttraumatic amnesia (PTA) and focal neurological deficits, such as visual disorders, hemiparesis or behavioural disorders without loss of consciousness.[6]

TBI results in different pathophysiological events that can lead to both focal and diffuse brain injury. Focal lesions caused by contusion or haemorrhage is an affection of a specific brain area that have specific functions which result in specific sequelae. The brain areas most vulnerable to damage of focal lesions are located in the frontal and temporal lobes.[10] Diffuse brain lesion often caused by diffuse axonal injury affects the whole brain resulting in more diffuse mental, physical and behavioural sequelae.[6,10] The diffuse axonal injury is caused by a sudden acceleration/deceleration of brain tissue or by rotational forces stretching the axons in the brain tissue.[10] Sometimes, TBI are classified as either caused by a closed head injury or a penetrating head injury.[6] Most brain injuries are due to closed head injuries, but severe blows to the head may cause penetrating or even open skull fractures. In such cases, both diffuse and focal brain lesions are likely to be found. Gunshot wounds and falls against sharp objects are examples of penetrating head injuries causing both focal and sometimes diffuse brain lesions.[6]

In the civilian population, TBI is primarily caused by falls and road traffic accidents, but age seems to have an impact on the main cause for TBI, as falls seems to be the primary reason for TBI in childhood, while TBI in adolescence and young adulthood primarily is caused by road traffic accidents.[5,11]

The severity of TBI is traditionally categorised as mild, moderate, and severe[6] and the most common classification is based on the Glasgow Coma Scale (GCS), which originally was developed to assess the depth of coma after head trauma.[12] The severity of TBI can also be classified based on length of PTA or length of loss of consciousness.[6] However, studies have shown that sequelae among patients with GCS>12 and an intracranial brain lesion seems to resemble the sequelae from moderate TBI rather than the sequelae from mild TBI, which has resulted in application of the term complicated-mild TBI.[13,14] Table 1.1 presents a classification of TBI severity.

Table 1.1: Classification of TBI severity

	Mild	**Complicated mild**	**Moderate**	**Severe**
Glasgow Coma Scale	13-15	13-15	9-12	3-8
Loss of consciousness	< 30 minutes	< 30 minutes	30 minutes – 24 hours	>24 hours
Post-traumatic amnesia	< 24 hours	<24 hours	1-7 days	>7 days
Structural imaging	Normal	Abnormal	Normal/ Abnormal	Normal/ Abnormal

Based on Cristofori & Levin (2015)[6], Kashluba et al. (2008)*[13], Kay et al. (1993)[15] & Teasdale & Jennett (1974)[12]*

The implementation of the term complicated mild TBI is a way to accommodate that GCS is widely used in the acute phase for evaluation and stratification of patients, but that patients with GCS>12 can have an intracranial lesion which could affect outcome.[13,16] Consequently, the term subdivides the large group of patients with mild TBI in relation to whether or not they have an intracranial lesion identified on structural imaging. The understanding of mild TBI have also been changed in the clinical setting, for example have the Scandinavian countries implemented a guideline that classify patients with head injury and GCS 13 or 14 into three categories: high-risk, medium-risk or low-risk of complications to the head injury.[17] This to ensure that the relevant patients are observed and/or scanned after the injury.[17] Furthermore, GCS might not be a good predictor of severity in relation to infants and young children, as

well as adults with pre-injury neurological or intellectual deficits,[6] as the GCS to a great extent relies on verbal comprehension and response. Nonetheless, assessment of TBI severity in the acute phase seems to predict outcome, as GCS at admission is associated with long-term employment probability and stability,[18,19] and PTA is associated with functional outcome after rehabilitation[20] as well as long-term outcome.[21]

1.1.1. INCIDENCE AND SOCIOECONOMIC CONSEQUENCES OF TRAUMATIC BRAIN INJURY

It is estimated that around 70 million individuals world-wide sustain a TBI each year, with the highest incidences in North America and Europe.[22] However, TBI caused by road traffic accidents seems to be highest in Africa and Southeast Asia, and study quality in the low- and middle-income countries might affect the reported incidence.[22] Based on European studies from 1998-2014 Peeters et al. (2015) found an overall incidence rate of 262 per 100,000 for admitted TBI of all severities.[3] In general, when studies include all TBI severities mild TBI accounts for most of the incidences, but the incidence varies from 71-97,5%.[3] In a global estimate study mild TBI accounted for 81% of the estimated incidence rate while moderate to severe TBI accounted for 19%.[22]

In Denmark, the incidence rate of moderate to severe TBI among adolescents and young adults have been decreasing from 1979 until 2013.[23,24] The incidence rate of first-ever hospitalization due to skull fracture, multiple fractures of facial bones or intracranial traumatic lesion among Danish adolescents and young adults (age 15-30 years) was 17.5/100,000 in 2013.[24] In Denmark, the relative frequency of contusion peaks at the age of 19 with a higher frequency among men (male: 36/100,000; women: 16/100,000).[11]

The total annual cost of TBI in Europe is estimated to €33 billion per year corresponding to an average cost of €8809 pr. patient, of which most patients have mild TBI and few patients have moderate to severe TBI.[25] The costs can be divided into direct health care costs, direct non-medical costs (rehabilitation in municipality, nursing home etc.) and indirect costs (absence from job/loss of job, social benefits etc.). For TBI the indirect costs account for 59.2% of the overall costs.[25] Furthermore, a recent Danish nationwide register-based study confirmed that socioeconomic consequences of TBI is evident years after the injury, as Norup et al. (2020) found that adults with TBI had increased health care costs 1-4 years after injury and an increased risk of job loss in the first three years after injury.[4]

1.2. SEQUELAE AND OUTCOME AFTER MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

1.2.1. EMOTIONAL SEQUELAE

Emotional sequelae are common after TBI, with substance abuse, mood disorder and anxiety disorder, including post-traumatic disorder (PTSD), being the most common psychiatric disorders after TBI.[26–29] Studies among adults with TBI have shown huge variations in the prevalence proportions of psychiatric disorders after TBI.[30] The existing literature on adults with TBI report prevalence proportions of depression that varies from 2% up to 80% of the study population,[31] and prevalence proportions of anxiety that varies from 9% to 50%.[30] The huge variations could be due to different assessment methods, different diagnostic criteria, pooling of TBI severities and variation in time-since-injury.[29,31]

Knowledge about psychiatric disorders among children and adolescents with TBI seems very sparse. In a systematic literature review Laliberté Dursh et al. (2017) identified 14 published studies about depression or depressive symptoms among children and adolescents (age 0-18 years) with TBI, in which the prevalence proportion of depression varied from 5.3% to 36%.[32] Furthermore, Iljazi et al. (2020)[33] identified 10 studies that reported on PTSD among children and adolescents with TBI, in which the prevalence proportion of PTSD ranged from 3.3% to 48.5%, and the analysis indicated that PTSD was more common among children and adolescents with severe TBI compared to mild TBI. Additionally, Arif et al. (2021)[34] found that paediatric TBI can have long-term consequences, as young adults with TBI in childhood/adolescence had a significantly higher rate of new-onset psychiatric disorder compared to a control group.

In relation to adults with moderate to severe TBI, Alway et al. (2016)[27] found that 3/4 of their study population received a psychiatric diagnose in the first 5 years post-injury. Additionally, the existing literature have shown that the prevalence proportion of anxiety was highest in the first year post-injury[27], while the prevalence proportion of depression was stable around 25% in the first five years post-injury.[27,35] However, studies have shown that depression can develop temporally close to the injury (identified 1 month post-injury)[36] as well as several years after the injury.[27,35] This means that a stable prevalence proportion of depression could conceal individual differences in development and remission of symptoms.[35]

As depression can develop temporally close to the injury as well as after the acute phase, indicate that depression could be a direct as well as an indirect consequence of the injury.[37] Depression caused by the injury could be related to inflammatory processes of the brain as well as changes in the white matter microstructure. Juengst et al. (2015)[38] found that acute inflammation due to the injury was associated with a higher risk of having depression 6 months post-injury, while Spitz et al. (2017)[39]

found an association between changes in the white matter microstructure and development of depression in the first 3 years post-injury. However, depression could also develop as a reaction to the changes in the functional abilities or to a severe course of illness, as well as due to problems with adapting to sequelae of the TBI.[37]

Taken together, new-onset psychiatric disorder seems to be common among children, adolescents, and adults with TBI, with depression and anxiety as the most common disorders. Consequently, identification and treatment of depression and anxiety after TBI seems very important, as both are associated with employment status[40,41], cognition[42,43], participation[42,44] and quality of life/life satisfaction.[36,45,46] The existing literature have identified pre-injury psychiatric disorder as risk factor for development of post-injury psychiatric disorder in children, adolescents and adults,[27,32,34] while symptoms of anxiety or depression in the acute phase and limb-injury also have been identified as risk factors in adults.[27,47] Identification of TBI-survivors with depression could be complicated by an overlap between the symptoms of depression and sequelae after moderate to severe TBI, for example can symptoms such as fatigue, altered cognitive function and sleep problems be related to both depression and TBI.[48]

1.2.2. COGNITIVE SEQUELAE

Cognitive impairment is a well-described sequela after moderate to severe TBI. Cognitive impairments are often described as heterogenous, but the most common cognitive sequelae seems to be changes in attention, executive function and memory.[49] This could be related to the fact, that the frontal lobes of the brain as well as the inferior temporal lobes seems to be most vulnerable to damage.[10] Attention seems especially vulnerable in relation to TBI, as attention is based on neural networks of different parts of the brain. Attention includes arousal, simple attention, and more complex attention processes, for example divided attention.[6] Executive functions are higher-order functions, such as planning, problem solving, initiation, inhibition and decision making, which are considered to be placed/organised in the prefrontal cortex (PFC).[6,49] Memory dysfunction can be caused by damage to hippocampus as well as the PFC, as PFC are involved in encoding and retrieval.[49]

The severity of the cognitive impairments are associated with the severity of the TBI, which is both the case for children, adolescents and adults.[5,6] Thus patients with severe TBI have more comprehensive cognitive impairments and recover more slowly than patients with moderate TBI, while patients with moderate TBI tend to have specific cognitive impairments and recover more slowly than patients with mild TBI (cf. figure 1.1).[6,50,51]

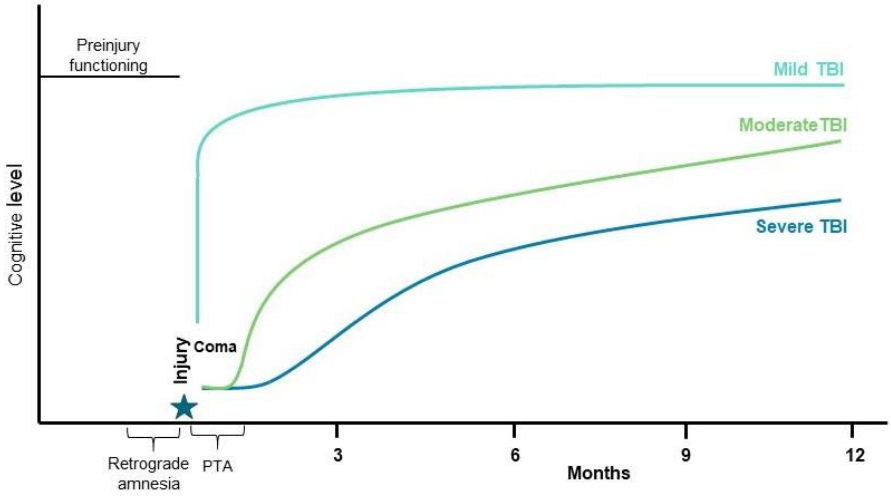

Figure 1.1 Schematic illustration of the temporal course of recovery after Cristofori & Levin (2015)[6]

Furthermore, studies have shown that the recovery of specific cognitive functions vary in relation to the cognitive domains as well as complexity.[52] Consequently, more complex cognitive functions recover more slowly than simple cognitive functions, thus simple attention seems to improve faster than more complex attention.[52,53] For example have Marsh (2019)[53] found a difference in recovery of attention due to the complexity of the task, as low impairment and continuous improvement from injury to five years post-injury was detected on a simple attention task, while no improvement was detected on a more complex attention task beyond the first year post-injury[53]

Overall, studies have determined that although patients with moderate to severe TBI do experience improvements in relation to cognition, many patients do not fully recover.[6,51,52,54,55] Lanno et al. (2001) identified three trajectories of neuropsychological improvement from trauma until 2 years post-injury. The first group had mild cognitive impairments after injury and improved slightly from injury to 2 years post-injury. The second and third group had severe cognitive impairments at baseline but differentiated in the recovery phase, as the second group improved considerable from injury to 6 months post-injury while the third group only improved a little from injury until 2 years post-injury.[54]

In general, the greatest improvement in cognitive functions is detected in the first 6 months after the injury, but for moderate to severe TBI improvement is detected several months and even years after the injury.[52,56,57] However, studies have also shown that some patients experience cognitive decline after the recovery phase.[53,57,58] Till et al. (2008) reported that as much as 27.3% of their study population had a significant cognitive decline on at least two neuropsychological tests 2-5 years post-injury compared to 1-year post-injury.[58] The deterioration seems to be heterogenous, as Marsh (2019) found that 12% of the study population had decline in relation to verbal memory at 5 years post-injury compared to the performance at 1-year post-injury[53], while Millis et al. (2001) found that 15.2% of the study population had cognitive decline on tasks requiring cognitive flexibility and speed at 5 years post-injury.[57]

Cognitive decline after the recovery phase could have different causes, such as age,[5,57,58] progression of brain atrophy[58] or depression.[59,60] Age at injury seems particularly important when looking at children and adolescents, as their brain is still developing at time-of-injury. The 'early vulnerability' model propose that the young brain is more vulnerable to damage of a diffuse injury as TBI[5], which is supported by Anderson et al. (1996) who determined that early childhood TBI (before age 7) was associated with worse cognitive outcome compared to later onset childhood TBI (at or later than 7 years).[61] Consequently, as the neural networks and the cognitive functions is not fully developed in children, they might be in risk of growing into cognitive difficulties when the specific cognitive function is supposed to develop.[5] Adolescents who sustain a moderate to severe TBI seems to have a better outcome than younger children. However, the prefrontal cortex is still developing and adolescents could be in risk of growing into difficulties with planning and judgement when daily life demands increases.[5]

Overall, cognitive outcome seems to differentiate due to individual as well as TBI-related factors, and might be dynamic, as both improvements and decline can occur even several years after the injury.[53,57] Furthermore, recovery of cognitive functions among adolescence and young adults could be influenced by the ongoing development of the brain.

1.2.3. GLOBAL FUNCTIONAL OUTCOME

Global functional outcome can be defined as the overall impact of the TBI on the global functional level and includes functional status, independence, as well as participation. Global functional outcome after moderate to severe TBI can be assessed in many ways, but the Glasgow Outcome Scale – Extended (GOS-E), Functional Independence Measure (FIM)[62] and Disability Rating Scale (DRS)[63] are the most commonly used assessment tools after moderate to severe TBI. GOS-E is identified as a core instrument when looking at long-term outcome[64], while FIM and DRS are

often used in the acute phase and inpatient rehabilitation, as they are developed to evaluate the disability of patients in rehabilitation and the progress of patients with severe TBI from coma to community.[62,63]

The existing literature have shown, that many patients with moderate to severe TBI experience improvements in their global functional outcome in the first-year post-injury[65], and that patients with moderate TBI do have a more favourable outcome compared to patients with severe TBI.[66,67] Sandhaug et al. (2015) found that global functional outcome assessed by GOS-E at 3, 12 and 24 months post-injury improved significantly over time for patients with moderate TBI, but not for patients with severe TBI.[66] Likewise, McCrea et al (2021) found that good recovery was present among 35% of the study population with moderate TBI, while only 22.9% of the study population with severe TBI experienced good recovery.[67]

However, studies on long-term global functional outcome indicate that outcome is a dynamic factor, with improvements and deterioration over time.[68–71] Forslund et al. (2019) found that 37% of the included adults with moderate to severe TBI had a lower GOS-E score at 10 years post-injury compared to 5 years post-injury, while only 7% had experienced improvement.[68] Furthermore, Whitnall et al. (2006) found that 29% of their study population had a higher GOS-E score at 5-7 years post-injury compared to 1-year post-injury, while 25% reported a decline.[70] Corrigan and colleagues (2014) showed that deterioration from 1-2 years post-injury until 5 years post-injury was present in all age-groups in the adult population, also among adolescents and young adults of whom around 1/3 experienced decline in the global functional outcome.[71]

Different factors are found to be related to long-term outcome.[68–70,72,73] Forslund and colleagues (2017 & 2019) found that individual factors such as younger age (<30), shorter PTA phase (<19 days) and employment at time of injury were associated with a higher GOS-E score at 5 and 10 years post-injury.[68,72] On the other hand, Whitnall et al. (2006) found that change in global functional outcome from 1-year post-injury to 5-7 years post-injury was associated with cognitive and emotional function assessed at the follow-up, but not age at injury (<40 years).[70] Furthermore, Ponsford et al. (2014) found that younger participants (≤50 years) were overrepresented in the severe disability group at 10 years post-injury compared to older participants (>50 years).[74] Taken together, younger age at injury seems not to be a protective factor by itself, which for adolescents and young adults might be related to that development of the brain seems to continue in adolescence and young adulthood.[75,76]

Overall, global functional outcome after moderate to severe TBI seems to be a dynamic factor with both improvement and deterioration over time. This could be because outcome after moderate to severe TBI is influenced by other factors in addition to the pathophysiological changes in the brain. This means that both direct and indirect factors such as depression, coping strategies and family status might influence outcome. The biopsychosocial perspective is a way to understand and

explain how outcome after moderate to severe TBI is affected by other factors than the pathophysiological changes in the brain.

1.3. THE BIOPSYCHOSOCIAL PERSPECTIVE

The biopsychosocial model (cf. Figure 1.2), was presented the first time by Engel[77] in 1977, and illustrate that the individual understanding of illness is affected by more than the specific illness (biological factors), as psychological and social factors also affects whether patients view themselves as sick. This means that patients differ from each other both in relation to the illness (biological factors) as well as in relation to psychological and social factors, which can affect how they understand and cope with their illness.[77]

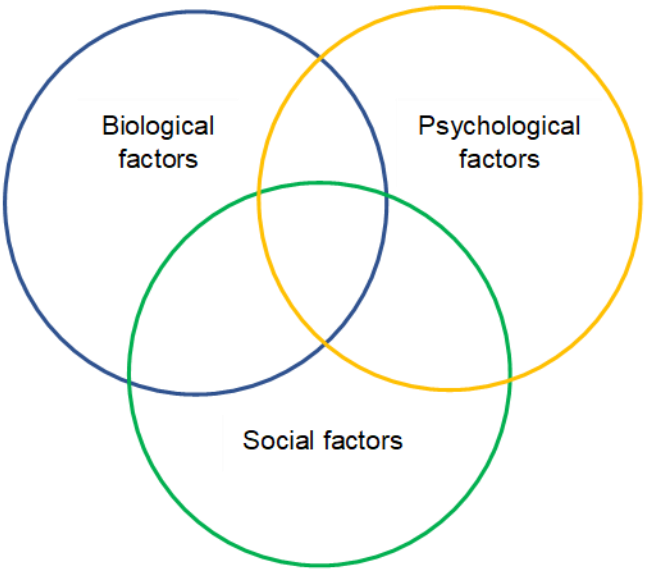

Figure 1.2: Illustration of the biopsychosocial model

Applied to outcome after moderate to severe TBI, this means that sequelae after moderate to severe TBI can be a direct and indirect consequence of the injury.[52] For example can cognitive sequelae be a direct consequence of the pathophysiological changes in the brain (biological)[49], but can also be an indirect consequence of the TBI, e.g. if the TBI-survivor develop a depression after the TBI (psychological factors), as depression can cause cognitive difficulties.[59] Accordingly, the biopsychosocial model seems appropriate to illustrate and understand the complexity of sequelae and outcome after moderate to severe TBI.

Another way to illustrate the interrelationship between biological, psychological and social factors is the International classification of functioning, disability and health (ICF) developed by the World Health Organisation (WHO) to accommodate a need for a classification of health and disability beyond mortality.[78,79] The ICF is a multidimensional framework, that is developed to give a mutual language and understanding of disability and functioning based on the biopsychosocial perspective. In the ICF functioning refers to body functions, activity, and participation, while disability refers to impairments, activity limitations, and restrictions in participation.[79]

The ICF framework provides a method to evaluate and understand body function, activity, and participation, which all can be affected by moderate to severe TBI. Furthermore, the framework illustrates the mutual interactions between health condition, contextual factors (personal and environmental factors), functioning and disability (cf. Figure 1.3).

Taken together, the biopsychosocial model and the ICF framework do illustrate that functional level/outcome after moderate to severe TBI can be affected by direct and indirect consequences of the TBI and that both biological as well as personal/psychological and environmental/social factors must be considered when evaluating outcome and planning rehabilitation/treatment.

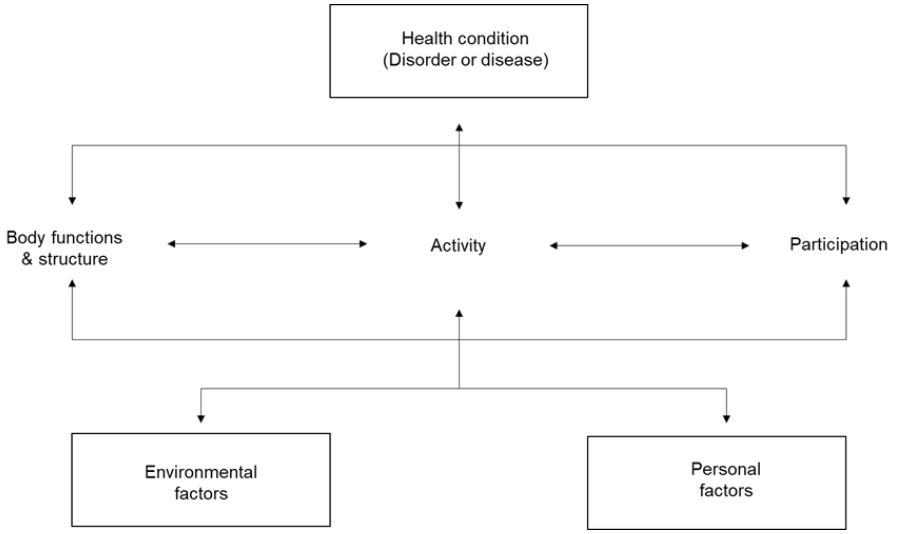

Figure 1.3: Illustration of the ICF framework (modified from WHO's webpage)[80]

1.4. ADOLESCENTS AND YOUNG ADULTS WITH MODERATE TO SEVERE TBI

Adolescents and young adults with moderate to severe TBI seem vulnerable due to biological, psychological, and social factors. The brain injury affects a brain that is still developing (c.f. section 1.2.3) and the young TBI-survivors will experience increased demands in their daily life, as adolescence and young adulthood are life periods characterized by many transitions.[81,82] The transitions include independency, education and labour-market attachment, as young people must separate from their parents, choose an education, and find a job. Furthermore, peers and being part of a peer-group is especially important in adolescence and young adulthood as well as it seems vital to do the same things as the peers.[82]

Hospitalisation and the possible sequelae after moderate to severe TBI might affect the transitions from a dependent child/adolescent to an independent young adult, and even make the young survivor dependent of the parents once again. Furthermore, the formation of identity might be complicated by the TBI, as there could be a conflict between the pre-injury identity and the post-injury identity.[83] Consequently, the young TBI-survivors might have to reconstruct their identity at the same time, as the formation of the identity is going on. Additionally, adolescents and young adults

might be in risk of losing contact to their peers, as studies have shown that social participation are reduced among adolescents and young adults with acquired brain injury (ABI) and TBI[84,85], and that young survivors of severe TBI might have a higher tendency to withdrawal compared to population-based norms.[86]

Furthermore, Di Battista et al. (2014) found that depression is a predictor for health-related quality of life among young TBI-survivors[87] and Tibæk et al. (2019) found a cumulative incidence of return to work at 85%.[88] However, only 50-60% of Danish young TBI-survivors had stable labour market attachment 1-10 years after the injury, which was significantly lower than a generated control group.[88]

Consequently, having a moderate to severe TBI in adolescence or young adulthood might result in an increased risk of not living an independent life, not obtaining an education, or a stable labour market attachment. Furthermore, young TBI-survivors might have a higher risk of developing depression or other psychiatric disorders compared to healthy adolescents and young adults. Accordingly, moderate to severe TBI might trigger a vicious spiral, in which direct and indirect consequences of the TBI affect the functional level/outcome in the long-term.

In general, the literature on adolescents and young adults with moderate to severe TBI seems relative sparse, as study populations primarily consist of children and adolescents (18 years and young)[32,89–91] or the entire adult population (age 16 or older).[27,52,68,92,93] Thus, it seems evident to get more knowledge about adolescents and young adults with moderate to severe TBI.

1.5. NATIONAL STUDY ON YOUNG BRAIN INJURY SURVIVORS

In 2012, the Danish Ministry of Health founded the national project 'National study on young brain injury survivors' to improve the evaluation of and counselling to adolescents and young adults with ABI (age 15-30 years). This, to ensure that young ABI survivors had the best possible conditions to achieve a good functional outcome after the ABI and to improve the cooperation between the hospitals and the young survivors' municipalities.[94]

Five regional outpatient clinics were established, offering young survivors of ABI an interdisciplinary examination after discharge. The clinical interdisciplinary teams consisted of doctors, neuropsychologists, physiotherapists, and occupational therapists. In some outpatient clinics, secretaries, social workers and/or coordinators were available. Beside the interdisciplinary examination the outpatient clinics established a close cooperation with the patients' municipalities, as they are responsible for all rehabilitation after discharge.[94,95]

To increase the knowledge about young survivors of ABI and to ensure a systematic collection of data the national clinical register 'Danish registry on young adults with acquired brain injury' (Danish acronym: DRUE – Dansk Register for Unge med Erhvervet hjerneskade) was established. DRUE consist of information on all young ABI survivors who were contacted by or referred to one of the five regional outpatient clinics in the period October 2013 to primo 2017 (Capital Region of Denmark and Region Zealand) or March/April 2014 to December 2016 (North Denmark Region, Central Denmark Region and Southern Denmark).[95]

CHAPTER 2. AIMS

Knowledge about sequelae and outcome after moderate to severe TBI among adolescents and young adults seems sparse and consequently, the main aim of this thesis is to improve knowledge about depression, cognitive sequelae, and outcome among adolescents and young adults with a moderate to severe TBI. This knowledge might help the young TBI-survivors, their relatives and the healthcare professionals in understanding the direct and indirect sequelae of the TBI and how this could affect outcome.

Accordingly, the thesis aims to answer the following research questions:

- Do young TBI-survivors differ from the general population regarding depression and use of antidepressants?
- Do the prevalence proportion of depression and cognitive sequelae change over time?
- Are depression and cognitive sequelae associated with outcome and/or return to work?
- Does the use of antidepressants among young TBI-survivors change over time?

The thesis focuses on the following hypothesis:

1. Knowledge about depression among adolescents and young adults are sparse.
2. Depression and use of antidepressants are more common among young TBI-survivors than in the general population.
3. Depression and cognitive sequelae are associated with a lower global functional outcome.
4. Depression and cognitive sequelae are negatively associated with return to work.

The research questions and hypothesis are addressed in the four studies, which have the specific aims:

Paper I: To do a retrospective survey of the existing knowledge on depression among adolescents and young adults with moderate to severe TBI.

Paper II: To determine the prevalence proportion of depression and cognitive sequelae after moderate to severe TBI among adolescents and young adults registered in DRUE and examined less than a year after the injury and to investigate whether depression and cognitive sequelae were associated with outcome at the first visit.

Paper III: To determine the prevalence proportion of depression and cognitive sequelae at the follow-up visit and to investigate whether depression and cognitive sequelae were associated with outcome and return to school/work.

Paper IV: To investigate the use of antidepressants from 1-year pre-injury until 5-years post-injury and to determine whether young TBI survivors differ from the general population regarding use of antidepressants.

CHAPTER 3. METHODS

This thesis is based on a systematic literature review **(Paper I)** and three original studies, which are based on data from the national clinical register DRUE **(Paper II and III)** and several nationwide registries **(Paper IV).**

3.1. STUDY DESIGNS

The study designs include a systematic literature review **(Paper I)**, a cohort-study **(Paper II)**, an observational 1-year follow-up study **(Paper III)** and a registry-based matched cohort study with logterm follow-up **(Paper IV)** (cf. figure 3.1).

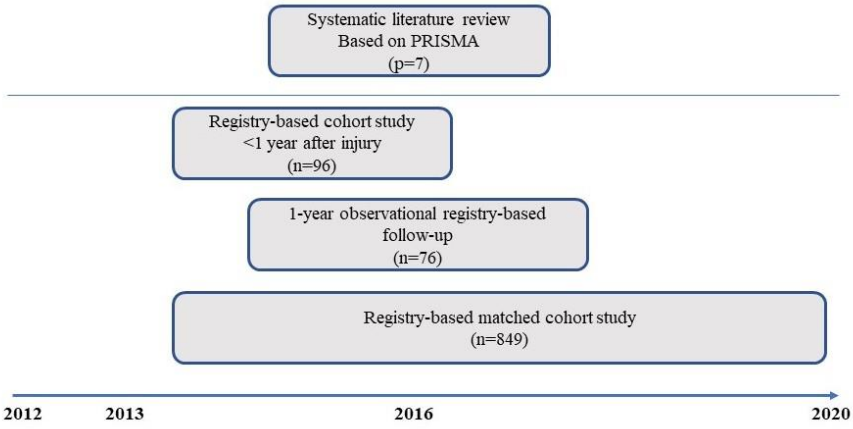

Figure 3.1: Study designs. p: included publications, n: included patients

3.2. STUDY POPULATION

The study population in this thesis is adolescents and young adults (age 15-30 years at the injury) with moderate to severe TBI. The specific in- and exclusion criteria for the four studies are presented in section 3.2.1-3.2.4.

3.2.1. THE SYSTEMATIC REVIEW (PAPER I)

Originally, the inclusion criteria were adolescents and young adults with moderate to severe TBI who were 15-30 years old at the injury, but as no studies in the systematic search had the exact age-range, the age-range was changed to 13-35 years at injury **(Paper I)**[96]. This to ensure that all relevant studies were included. Studies with a wider age-range were included if a prevalence proportion of depression could be extracted within the chosen age-range **(Paper I)**[96].

Moderate to severe TBI was defined as 1) an acute Glasgow Coma Scale GCS score below 13[12,97] or 2) an acute GCS score above 12 and an abnormal computed tomography scan of cerebrum.[13] Studies were also included if the population were defined as having moderate to severe TBI although the definition of injury severity were not stated or deviated from the above-mentioned definition **(Paper I)**[96].

3.2.2. THE DRUE-TBI COHORT (PAPER II AND III)

Danish adolescents and young adults were registered in DRUE if they 1) had an ABI caused by TBI, stroke including subarachnoid haemorrhage, encephalopathy, central nervous system infection or primary brain tumour, 2) were referred to one of the five outpatient clinics and 3) were 15-30 years of age at time of referral.[95] An ABI was defined as a brain injury occurred after the 27th day after the birth with no restriction in relation to time-since-injury.[95] The specific including diagnostic codes according to the International Classification of Diseases, 10th revision (ICD-10)[98] are presented in Appendix A.

The DRUE-TBI cohort was defined as patients in DRUE with an intracranial traumatic lesion diagnostic code (ICD-10, S06.1-S06.9 and T90.5, cf. Table 1 in **Paper II**) who were referred to one of the five regional outpatient clinics in the period October 2013 to December 2016 and invited to an interdisciplinary examination less than a year after the injury **(Paper II).**[99]

The identification was based on 1) the diagnostic code assigned by the medical doctor after the interdisciplinary examination and 2) the time from injury to the date of the first interdisciplinary examination **(Paper II).**[99] For non-attendees the referral diagnosis group and date of visitation were used for identification.

Patients in the DRUE-TBI cohort (N=131) were included in the cohort study (**Paper II**) if they had complete data on MDI, GOS-E and the eight neuropsychological tests at the first visit at the outpatient clinics (N=96).[99] Patients were included in the one-year follow-up study (**Paper III**) if they had complete data on MDI, GOS-E and the eight neuropsychological tests at the first visit and at the follow-up visit approximately

one-year after the first visit (N=79) **(Paper III)**. The flow-chart for inclusion in the cohort study (**Paper II**) and the one-year follow-up study (**Paper III**) is presented in figure 3.2.

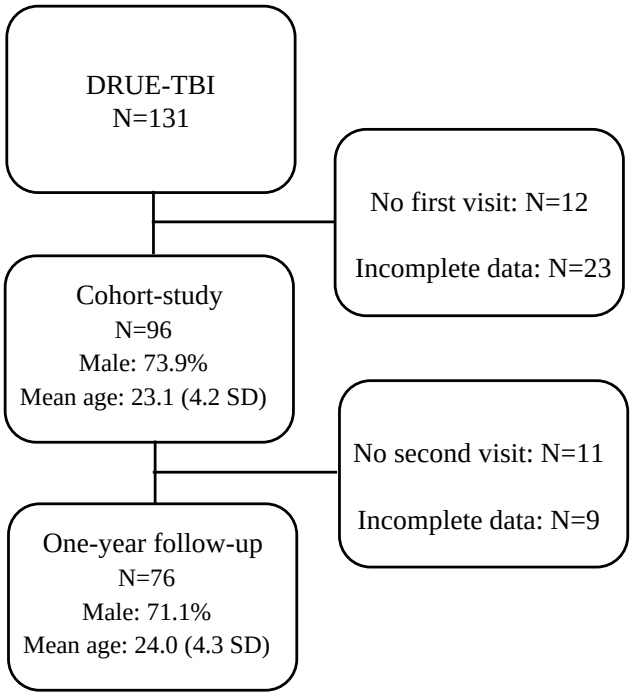

Figure 3.2: Flowchart illustrating the inclusion in the cohort study (Paper II) and the one-year follow-up study (Paper III)

3.2.3. THE MATCHED COHORT STUDY (PAPER IV)

The registry-based matched cohort study with long-term follow-up included 1) a TBI-population identified by Statistics Denmark, which was divided into the TBI+DRUE and the TBI÷DRUE subpopulations, and 2) a general population matched control group generated by Statistics Denmark **(Paper IV)**.

TBI-population

The TBI-population was defined as **all** Danish adolescents and young adults (age 15-30 years) who in the period June 01, 2013 to October 31, 2016 were admitted to a Danish hospital and had one of the following ICD-10 diagnostic codes S06.1-S06.9

registered in the National Patient Register (NPR)[100] or in DRUE[95] (n=880) **(Paper IV)**. Furthermore, the patients had to have a 'Highest education attained' registered in the register of Highest education attained[101] to be included in the study (n=849) **(Paper IV)**. The flowchart for the TBI-population is presented in figure 3.3. Patients who died or migrated from Denmark in the 5-year follow-up period were censored at time of death/migration **(Paper IV)**.

TBI+DRUE

The TBI+DRUE subpopulation consists of patients in the TBI-population who were registered in DRUE and attended at least the first interdisciplinary examination at one of the five outpatient clinics (n=162) **(Paper IV)**. Patients not registered in DRUE are identified as TBI÷DRUE (n=687).

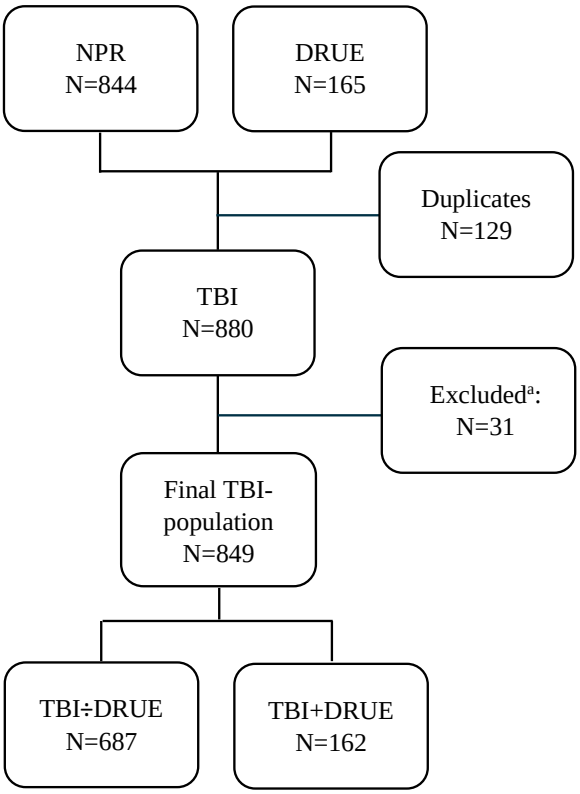

Figure 3.3: Flowchart of the TBI-population.
[a]Excluded as a highest education attained at injury were not registered.
Adopted from Ryttersgaard et al. ***(Paper IV).***

General population matched controls

The general population matched controls consisted of Danish adolescents and young adults who matched the TBI-population 1:10 according to birth year, sex and highest education attained at time of injury (called index) (n=8490) **(Paper IV)**. Statistics Denmark used matching with replacement when generating the control group.

3.3. DATA SOURCES (PAPER I-IV)

3.3.1. SYSTEMATIC LITERATURE SEARCH (PAPER I)

The systematic literature review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and meta-analyses) guidelines[102] and a systematic review protocol was developed before the search was conducted (cf. Supplementary materials in **Paper I**).[96]

The systematic search was conducted in the PubMed database, Embase, PsychInfo and Cochrane on January 16th, 2018, and updated December 14th, 2018 (Literature search strategies are presented in Appendix A in **Paper I**). In addition, reference lists of included articles and relevant reviews were analysed to identify additional relevant citations **(Paper I)**[96].

3.3.2. DANISH REGISTER FOR YOUNG ADULTS WITH ACQUIRED BRAIN INJURY (PAPER II AND III)

Danish register for young adults with acquired brain injury (DRUE) contains administrative and clinical data on young survivors of ABI who were contacted by or referred to one of the five outpatient clinics.[95] The administrative data contains information about the patients, e.g. gender, date of birth and date of injury. The clinical data contains information about the patients' functional level, e.g. diagnosis, cognitive, physical and emotional function, as well as fatigue, education and job situation. The administrative data was primarily collected from the patients' medical record, while the clinical data was collected at two interdisciplinary examinations, one after referral and one approximately one-year after the first visit.[95] Data from DRUE included in Paper II and III are described below.

Demographics: Demographics such as gender, date of birth, date of injury and date of the first visit as well as the one-year follow-up were retrieved from DRUE.

Depression: Major depression inventory (MDI) was used to determine whether the patients fulfilled the ICD-10 diagnostic criteria for depression.[103–105] The number of core symptoms, associated symptoms and the total score from the first visit as well as the one-year follow-up were available in DRUE.

MDI is a self-report inventory which is developed to determine depression based on the patients' self-reported symptoms. The inventory consists of 12 symptom-questions, which are rated on a six-point Likert-deviation scale: 'All the time', 'Most of the time', 'Slightly more than half the time', 'Slightly less than half the time', 'Some of the time', or 'At no time'.

Sensitivity and specificity of the MDI have not been assessed in TBI patients. In a group of subjects with depressive symptoms the specificity was between 0.82 and 0.86 and the sensitivity was between 0.86 and 0.92.[103]

Cognitive sequelae: Cognitive sequelae were defined as minimum two performances 2 standard deviations (SD) below the best available Danish population-based norms or non-completion due to cognitive difficulties (registered as "Could not complete") on the eight neuropsychological tests.[106] The definition of cognitive sequelae was chosen to avoid mistaken interpretation of one performance 2 SD below the mean, as the patients' pre-injury level of cognitive functioning was not available in DRUE,[95,106] and as Binder et al (2009) have shown that healthy adults can have scores 2 SD below the mean.[107]

Performances on the eight neuropsychological tests: Trail Making Test A (TMT-A) and B (TMT-B)[108], Word-learning with selective reminding – learning and memory[109], Fluency – category and letter[110], as well as Coding and Matrix reasoning from Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV),[111] from the first visit and the one-year follow-up visit were retrieved from DRUE.

The neuropsychological tests were administered and scored by neuropsychologists at the five outpatient clinics. However, no information is available about how many neuropsychologist that administered and scored the tests, and whether it was the same neuropsychologist who administered both tests.[95]

TMT-A, TMT-B and Coding measure processing speed and attention,[108,111] Word-learning with selective reminding measures verbal learning and memory,[109] Fluency – category and letter measure fluency and Matrix reasoning measures perceptual reasoning.[110,111] The best available Danish population-based norms were used to evaluate the performances. For TMT-A and -B, Wordlist with selective reminding and Fluency the age-group 20-29 was used as reference group[112], while the age-group 20-24 was used for Coding and Matrix Reasoning from WAIS-IV.[111]

Global functional outcome: The Glasgow outcome scale – extended (GOS-E) was used to evaluate the patients' global functional outcome.[113,114] GOS-E is a structured interview that classify the patients overall global functional outcome in eight categories: Dead, vegetative state, lower severe disability, higher severe disability, lower moderate disability, higher moderate disability, lower good recovery and higher good recovery, equalling a score from one to eight.

GOS-E score from the first visit and follow-up were retrieved from DRUE. Information on whether the professional who made the GOS-E interview were blinded to other relevant study measures, how many raters that participated and whether the raters were trained are not described.[106] Furthermore, inter-rater reliability were not available.[106]

Rehabilitation between the first visit and the one-year follow-up: Information about rehabilitation was collected at the follow-up visit using a semi-structured interview.[115] Rehabilitation was defined as all services initiated by the young survivors' municipalities between the two visits with the purpose to improve functioning and reduce the experience of disability.[115]

Information about rehabilitation between the first visit and follow-up for example in relation to activities of daily living, educational or work skills and cognition was retrieved from DRUE. The extent and intensity of the rehabilitation are not available in DRUE.

Return to work/school at one-year follow-up: Return to work/school (RTW) was defined as having an employment or being enrolled in education without being absent due to illness. There was no distinguish between full or parttime job. Self-supportive labour market attachment and flexi-job (welfare supported labour market attachment) were defined as employment, while absent due to illness, unemployment or early retirement was defined as not returned to work **(Paper III)**.

Information about employment status and whether the young TBI-survivors were absent from job/school due to illness at the first visit and at follow-up was retrieved from DRUE. The information was collected using a self-report questionnaire constructed to DRUE. [116]

3.3.3. DANISH NATIONAL REGISTERS (PAPER IV)

The Danish Civil Registration System

The Danish Civil Registration System (DCRS) was established in 1968 and contains information about all persons who are born alive of a mother registered in DCRS, who have their birth/baptism registered in a Danish electronic church register, or who have legally residence in Denmark for 3 month or more.[117]

When registered a person receives a 10-digit Civil Personal Register number (CPR), which makes it possible to link data from all national registries. Beside the personal CPR number, DCRS also contains information on migration and vital status (date of death, emigration and disappearance).[117] The data is updated on daily basis Monday to Friday.

Information about CPR as well as time of death and migration from Denmark were retrieved from the register.

The Danish National Patient Register

The Danish National Patient Register (NPR) was established in 1977 with data on somatic inpatients.[100] Today the register include data on somatic and psychiatric in- and outpatients. The register consists of two types of information: Administrative data and clinical data. The administrative data contains information about the patients e.g. CPR number, hospital ward as well as date and time of activity, while the clinical data include information about diagnosis and surgical procedures.[100]

As the register has undergone many changes over time the validity of the data rely on the researchers awareness about the changes: ICD-10 diagnostic codes have been used since 1994,[100,118] and data from public hospitals has been complete since 2000.

The TBI-population was identified in NPR by Statistics Denmark. Information about TBI-diagnosis at injury was retrieved from the register when available.

The Danish National Prescription Registry

The Danish National Prescription Registry was established in 1994 and contains information about dispensed medical prescriptions on an individual level.[119] The Danish National Prescription Registry is unique as it contains information about the Danish nations medical use over a long time period.

Information about dispensed antidepressant (ATC=N06A) was retrieved from the register in the period 2012 - June 2021.

Highest education attained

The register 'Highest education attained' contains information about Danish citizens highest education attained.[101]

Information about highest education attained at injury/index was used as matching variable.

The Population

The Population contains among other things information about date of birth, sex, family type, municipality, and marital status. The Population is electronic available from January 1st, 1976.[120]

Information about sex and date of birth were retrieved from the register.

3.4. RISK OF BIAS ASSESSMENT (PAPER I)

As the included studies in the systematic literature review (**Paper I**) primarily consisted of observational studies, no specific Risk of Bias (RoB) assessment tool was recognised as suitable. Thus, criteria for the RoB assessment were developed based on the principles of Agency of Health Research and Quality[121], which is based on Cochrane Handbook of Systematic Reviews.[122]

The criteria for the RoB assessment is presented in Table 1 in **Paper I**[96].

3.5. STATISTICAL ANALYSIS

Prevalence proportion of depression and cognitive sequelae with 95% Confidence Interval (CI) were calculated at the first visit (**Paper II**) and at the follow-up visit (**Paper III**). Furthermore, at the follow-up visit prevalence proportion of rehabilitation between the two visits was calculated with 95% CI (**Paper III**). A one-sample test of proportion was used to determine whether the proportion of cognitive sequelae differentiated from the expected proportion (2.2%) in the general population of adolescents and young adults, which was identified based on the Normal distribution (Bell curve) (**Paper II** and **III**). Additionally, the Two-sample Wilcoxon test was used to evaluate whether the performance on the neuropsychological tests at the first visit differed between the depressed group and the non-depressed group (**Paper II**). For this analysis patients registered with "Could not complete" were assigned a score one worse than the worst performance in the study population.[123]

In **Paper II** and **III**, the Two-sample Wilcoxon test was used to determine whether the global functional outcome among patients with depression and/or cognitive sequelae differed from the global functional outcome among patients without depression and cognitive sequelae.

In **Paper III** the Chi^2-test was used to examine whether there were an association between depression/cognitive sequelae and RTW. Furthermore, the Wilcoxon Signed-rank test was used to examine whether the GOS-E score had changed from the first visit to the one-year follow-up (**Paper III**). Additionally, positive and negative changes of 1.5 SD or more on the neuropsychological tests were identified based on the best available Danish population-based norms.[111,112]

In **Paper IV** we used repeated measures ANOVA (Analysis of variance) to investigate whether dispensed antidepressants differed between the TBI-population and the matched control group, as well as between the TBI+DRUE and the TBI÷DRUE subpopulations. The analyses were done in periods of 180-days intervals from 360 days pre-index until 5-years post-index. We adjusted for age at index, as the year of birth was used for matching. Patients and controls who died or migrated from Denmark in the follow-up period were censored at time of death/migration. The results are presented in Margins plots.

Analyses used a two-tailed significance level of $p<0.05$, and results are presented with 95% CI. Data was analysed using Stata, version 15.0[124] (**Paper II**), Stata version 16.0[125] (**Paper III**) and Stata version 17.0[126] (**Paper IV**).

CHAPTER 4. SUMMARY OF RESULTS

4.1. SYSTEMATIC REVIEW – DEPRESSION AMONG ADOLESCENTS AND YOUNG ADULTS WITH MODERATE TO SEVERE TBI (PAPER I)

Seven studies were identified as reporting on prevalence proportion of depression among adolescents and young adults with moderate to severe TBI. The Prisma-flowchart is presented in figure 1 in **Paper I**[96].

The seven studies reported prevalence proportions of depression that varied from 1.6%[127] to 60%[128,129] **(Paper I)**.[96] Table 4.1 shows study characteristics and the respective prevalence proportion of depression from the seven included studies.[36,74,127–131]

The Risk of Bias (RoB) assessment showed that the seven studies had between one[74] and five[131] high risk assessments (cf. figure 2 in **Paper I**).[96] The included studies were primarily single-centre studies (5/7), most of the studies did not report on attrition analysis (6/7) and 4/7 studies did not describe their recruitment process. Consequently, a pooled prevalence proportion of depression was not calculated **(Paper I)**.[96]

Table 4.1 Study characteristic of the seven identified studies.

Author, year, country, design	Study population	Sample	Assessment	Prevalence (%)	95% CI	Follow-up mean (SD), *range*
Bombadier, 2010[132]**, US, Prospective**	Compl. mild to severe TBI, Level 1 trauma centre, (n=175)	18-29y Demographics not available for 18-29y	Structured interview based on PHQ-9	52.6[b]	44.9-60.2	1m, 6m, 8m, 10m, 1y
Garske,1992[130]**, US, Cross-sectional**	Severe TBI, Acute rehab. centre, (n=47)	22.9y (5.5), 16-35; male 68%	BDI	55.3	40.1-69.8	49.9m (22.2), *16-97m*
O'Connor, 2012[127] **US, Prospective**	Compl. mild to severe TBI, Nine hospitals, (n=64)	Age is not available for the incl. groups. male 72%	PHQ-9	1.6	0.0-8.4	3m, 1y, 2y
Poggi, 2003[131]**, Italy, Cross-sectional**	Moderate to severe TBI Rehab. Centre, (n=64)	15.8y (1.48), 14-18; Male 77%	The first scale of the TAD	13	5.6-23.2	1y
Tyerman, 1984[128]**, UK, Cross-sectional**	Severe TBI Rehab. centre, (n=22)	22y[a], 17-34; male 93%	The Leeds Scale of Depression	60	36.4-79.3	7m, *2-15m*
van Reekum, 1996[129]**, Canada, Cross-sectional**	Mod. to severe TBI incl., Rehab. program, (n=10)	23.4y[a], 19-30; male 60%	Semi-structured interview SADS-L	60	26.2-87.8	4.9y, *2-9y*
Willmott, 2015[74]**, Australia, Cross-sectional**	Compl. mild to severe TBI; Rehab. centre, (n=145)	18.6y (3.29), 13-34; male 64.1%	The Struct. Outcome Question.	39.3	31.3-47.8	1y

BDI: Beck Depression Inventory; PHQ-9: Patient Health Questionnaire-9; SADS-L: Schedule of Affective Disorder and Schizophrenia-L; TAD: Test of Anxiety and Depression in childhood and adolescence; UK: United Kingdom; US: United States of America; m=month, y = year; [a]Age at assessment, [b]Met criteria for Major depression disorder in minimum one of 5 assessments during the first-year post-injury.

Constructed based on table 2 and table 3 from Ryttersgaard TO, Johnsen SP, Riis JØ, Mogensen PH, Bjarkam CR. Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review. Scandinavian Journal of Psychology, 2020, 61(2), p. 297-306 ***(Paper I)***.[96]

4.2. DEPRESSION AND COGNITIVE SEQUELAE WITHIN THE FIRST YEAR AFTER INJURY (PAPER II)

The 96 patients included in the cohort study were mainly male (73.9%), had a mean age of 23.1 years at injury (SD: 4.2, range 15.3-31.1) and visited one of the outpatient clinics on average 170.8 days after injury (cf. table 1 in **Paper II**).[99]

Of the 96 included young TBI survivors 14.6% (95% CI: 8.2-23.3) fulfilled the ICD-10 criteria for depression and 34.4% (95% CI: 25.0-44.8) fulfilled the definition of cognitive sequelae. The prevalence of cognitive sequelae differed significantly from the expected 2.2% in the general population ($z=21.49$, $p<0.0001$) **(Paper II)**.[99] Additionally, an association was found between depression and cognitive sequelae ($p=0.002$) and the depressed group (n=14) had a mean indicating a worse performance on seven of the eight neuropsychological tests compared to the non-depressed group (n=82) (cf. table 4.2) **(Paper II)**.[99]

Regarding the global functional outcome, more than half of the study population had a GOS-E score of 5 and 6 (61.5%, 95% CI: 51.0-71.2), equalling moderate disabilities, while only 24.0% (95% CI: 15.8-33.7) of the study population had a GOS-E score of 7 or 8 equalling good recovery. The distribution of the GOS-E score at the first visit is presented in figure 4.1 **(Paper II)**.[99]

Additionally, patients with depression and cognitive sequelae (n=10) had a lower mean GOS-E score compared to patients without depression and cognitive sequelae (n=59), with an absolute mean difference on GOS-E at 1.6 (95% CI: 0.8-2.4, $z=3.987$, $p=0.0001$, n=96) **(Paper II)**.[99]

Table 4.2 Comparison of the neuropsychological performances in the depressed group vs. the non-depressed group.

Neuropsychological test	Non-depressed n=82	Depressed n=14	Z	p-value
Trail Making A	30.6 (12.5)	40 (19.4)	-2.556	0.0106*
Could not complete	0/82	1/14		
Trail Making B	79.4 (36.2)	138.4 (71.2)	-3.115	0.0018**
Could not complete	1/82	3/14		
Coding WAIS-IV	58.6 (14.84)	42.4 (20.41)	2.977	0.0029**
Could not complete	1/82	3/14		
Selective reminding - learning	82.8 (14.6)	65.7 (23.1)	2.619	0.0088**
Could not complete	4/82	5/14		
Selective reminding - memory	8.1 (2.2)	5.4 (3.1)	3.262	0.0011**
Could not complete	4/82	5/14		
Fluency - category	20.6 (5.6)	17.3 (6.3)	2.045	0.0409*
Could not complete	1/82	1/14		
Fluency - letter	11.4 (4.6)	11.4 (4.1)	-0.057	0.9544
Could not complete	1/82	1/14		
Matrix reasoning	17.8 (4.0)	14.2 (4.5)	2.923	0.0035**
Could not complete	0/82	1/14		

*Patients registered as "Could not complete" were assigned a score one worse than the worst score in the study population (cf. Statistical analysis). *p<0.05 **p<0.01*
Adopted from Ryttersgaard TO, Riis JØ, Johnsen SP, Mogensen PH, Bjarkam CR. (2020). Depression and cognitive sequelae registered within the first year among young Danish TBI survivors. Scandinavian Journal of Psychology, 61(5), 663–670. ***(Paper II)***

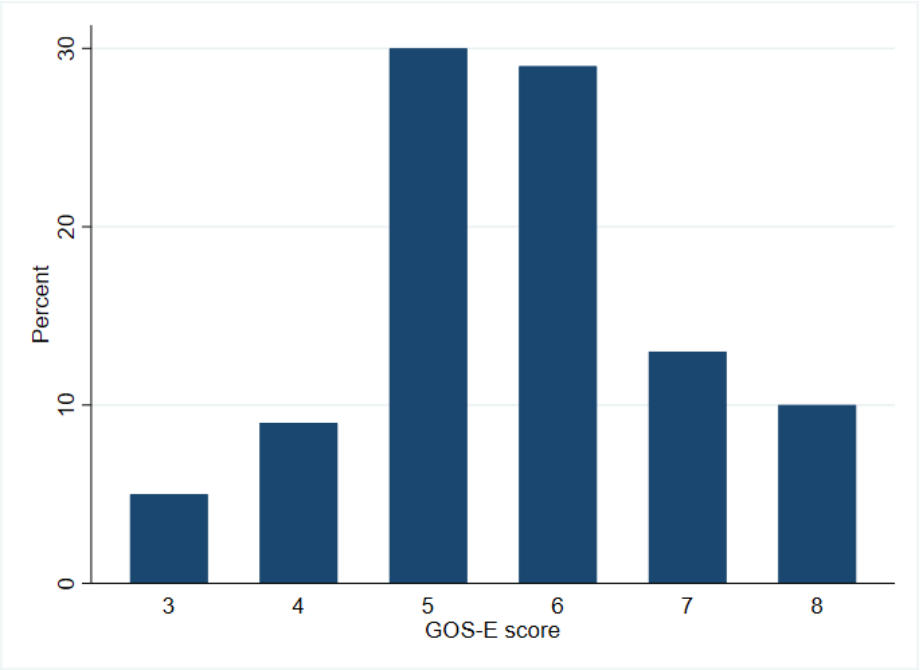

Figure 4.1: Distribution (%) of GOS-E score at the first visit (n=96)
Adopted from Ryttersgaard TO, Riis JØ, Johnsen SP, Mogensen PH, Bjarkam CR. (2020). Depression and cognitive sequelae registered within the first year among young Danish TBI survivors. Scandinavian Journal of Psychology, 61(5), 663–670. ***(Paper II)***

4.3. FOLLOW-UP ONE-YEAR AFTER THE FIRST VISIT (PAPER III)

Of the 96 patients included in the cohort study (**Paper II**), 76 (79.2%) were included in the observational 1-year follow-up study, as they attended the follow-up approximately one-year after the first visit and had complete data **(Paper III)**. The study population consisted primarily of males (71.1%) with a mean age of 24.0 (SD 4.3, range 16.4-33.3) at the follow-up visit and the mean time from the first visit to follow-up was 396.9 days (SD 53.6, range 307-594) (cf. Table 1 in **Paper III** for demographics) **(Paper III)**.

Although, the prevalence proportions of depression and cognitive sequelae were lower at the follow-up visit compared to the first visit, none of the differences were significant. The prevalence proportion of depression was 10.5% (95% CI: 4.7-19.7) at the one-year follow-up compared to 14.5% (95% CI: 7.5-24.4) at the first visit. Furthermore, the prevalence proportion of cognitive sequelae was 19.7% (95% CI:

14.5-30.5) at the follow-up visit compared to 31.6% (95% CI: 21.4-43.3) at the first visit **(Paper III)**. The prevalence proportion of cognitive sequelae at the follow-up visit differed significantly from the expected 2.2% in the general population ($z=10.4226$, $p<0.0001$).

As presented in table 4.3 both improvement and decline of the performance on the specific neuropsychological tests were detected. Positive and negative changes of 1.5SD or more were primarily detected on neuropsychological tests that measure processing speed and attention, as well as verbal learning and memory.

Table 4.3 Distribution (%) of negative and positive change on the specific neuropsychological tests from the first visit to follow-up visit.

	Negative change (≥ -1.5SD)	**Positive change (≥ +1.5SD)**
Trail Making Test A (n=76)	9.2	11.8
Trail Making Test B (n=74)	16.2	13.5
Coding (n=74)	0	0
Selective reminding – learning (n=70)	8.6	14.3
Selective reminding – memory (n=70)	12.9	20
Fluency – animal (n=76)	<3.9	<3.9
Fluency – letter (n=75)	<4	5.3
Matrix reasoning (n=76)	3.9	9.2

Sixty-six of the included patients (86.8%) reported that they had participated in rehabilitation between the first visit and the follow-up visit. Of these, 83.3% reported that they had participated in more than one kind of rehabilitation. Figure 4.2 shows the distribution of rehabilitation initiatives **(Paper III)**.

The GOS-E score was significantly higher at the follow-up visit compared to the first visit (z= -3.373, p=0.0007) and 42.1% (95% CI: 30.9-54.0) had a higher GOS-E score at the follow-up. However, 14.5% (95% CI: 7.5-24.4) had experienced deterioration in the GOS-E score from the first visit to the follow-up **(Paper III)**. Figure 4.3 shows the distribution of GOS-E scores at the first visit and the follow-up visit approximately one-year after the first visit.

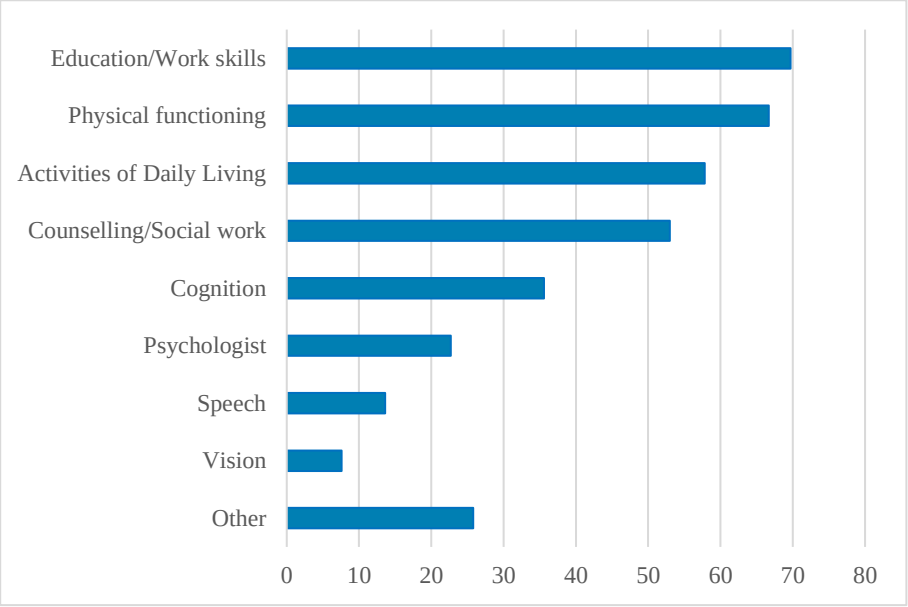

Figure 4.2: Distribution in % of rehabilitation initiatives between the first visit and the follow-up visit (n=66)

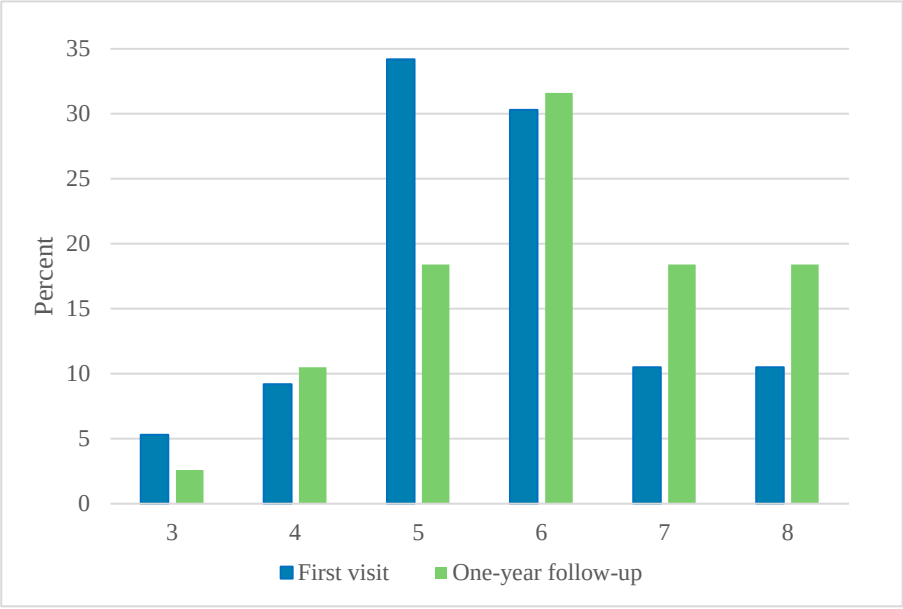

Figure 4.3 Distribution of GOS-E score (3-8) at the first visit and the follow-up visit (n=76)

At the follow-up visit, young TBI-survivors with depression and/or cognitive sequelae (n=21) had a lower mean GOS-E score compared to the young TBI-survivors without depression and cognitive sequelae (n=55), with an absolute mean difference on 1.1 (95% CI: 0.5-1.7, z=3.160, p=0.0016) **(Paper III)**.

Additionally, among the 66 young TBI survivors who were in school or had a job before the injury, only 59.1% had returned to work or school at the follow-up visit and an association was found between depression/cognitive sequelae and RTW (Pearson chi2(1) = 4.0169, p=0.045) **(Paper III)**. The young TBI-survivors with depression and/or cognitive sequelae were less likely to have returned to work/school compared to the young TBI-survivors without depression and cognitive sequelae (36% vs. 65%) **(Paper III)**.

4.4. USE OF ANTIDEPRESSANTS (PAPER IV)

The nationwide matched cohort study included 849 Danish adolescents and young adults with an intracranial traumatic lesion. The TBI-population consisted primarily of males (67.7%) and the median age at injury were 22.5 years (cf. Table 1 in **Paper IV) (Paper IV)**.

The TBI-population had a higher prevalence proportion of dispensed antidepressants (7.4%, 95% CI: 5.7-9.4) in the year before the injury compared to the matched control group (4.4%, 95% CI: 4.0-4.9) **(Paper IV)**. The TBI+DRUE and the TBI÷DRUE subpopulations resembled each other on sex, age at injury and dispensed antidepressants in the year before the injury. The distribution of the TBI diagnostic codes differed between the two subpopulations, primarily as more of the TBI÷DRUE had a diffuse traumatic brain injury (ICD-10: S06.2), or an unspecified intracranial injury (ICD-10: S06.9) registered in NPR (cf. Supplementary materials in **Paper IV) (Paper IV)**. However, it must be considered that the TBI diagnostic code was not available for 21% of the TBI+DRUE subpopulation **(Paper IV).**

The TBI-population had a consistently higher prevalence proportion of dispensed antidepressants from injury to 5 years post-injury compared to the general population matched controls (cf. figure 4.4.1 and 4.4.2) **(Paper IV)**. For the TBI-population the prevalence proportion started to increase before index and peaked at 12–18 months post-injury (“360 days since index”) with a prevalence proportion at 10.5% (95% CI: 9.2-11.9) **(Paper IV)**. In comparison the prevalence proportion was 3.4% (95% CI: 2.9-3.8) for the general population matched controls at the same time-point. The TBI-population had a relative stable prevalence proportion around 9% from 18 months post-injury to 5 years post-injury, while the prevalence proportion in the general population matched controls peaked with 4.6% (95% CI: 4.2-5.1) at 4.5 years post-injury **(Paper IV)**.

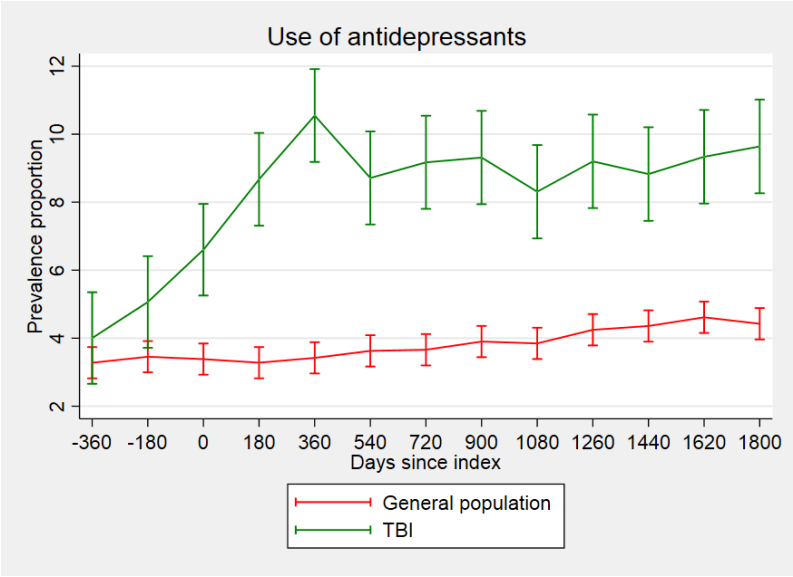

Figure 4.4.1: The prevalence proportion of dispensed antidepressants in the TBI-population and the general population matched control group. "0 days since index" corresponds to the period from index until 180 days post-index and so on. Adopted from Ryttersgaard et al. (Paper IV)

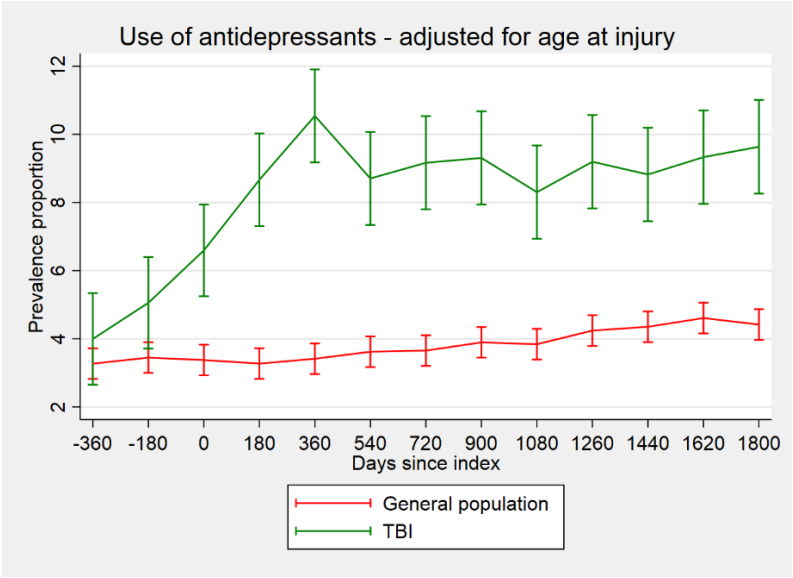

Figure 4.4.2: The prevalence proportion of dispensed antidepressants – adjusted for age at index in the TBI-population and the general population matched control group.
"0 days since index" corresponds to the period from index until 180 days post-index and so on. Adopted from Ryttersgaard et al. (Paper IV)

The TBI+DRUE and the TBI÷DRUE subpopulations did not differ in the prevalence proportion of dispensed antidepressants at any time-point in the unadjusted model (cf. figure 4.5.1) **(Paper IV)**. However, the TBI+DRUE subpopulation had a higher prevalence proportion of dispensed antidepressants from 1-year post-injury (’360 days since index’) to 2.5-years post-injury (’720 days since index’) compared to the TBI÷DRUE subpopulation, when adjusting for age at injury (cf. figure 4.5.2) **(Paper IV)**. The TBI+DRUE subpopulation had a peak in the prevalence proportion at 360 days since index corresponding to 12-18 months post-injury at 15.7% (95% CI: 11.5-19.9), while the TBI÷DRUE at the same time-point had a prevalence proportion of 9.3% (95% CI: 7.2-11.3) **(Paper IV)**.

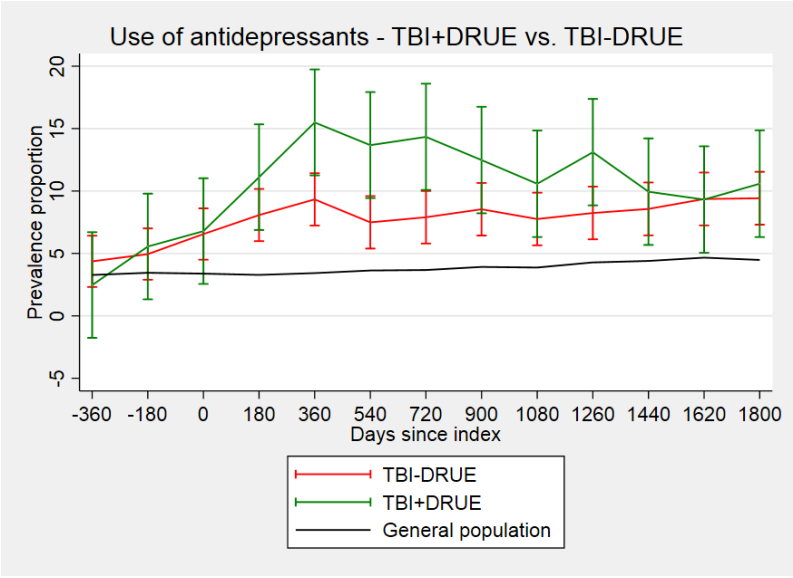

Figure 4.5.1: The prevalence proportion of dispensed TBI+DRUE and the TBI-DRUE subpopulations.
"0 days since index" corresponds to the period from index until 180 days post-index and so on. Adopted from Ryttersgaard et al. (Paper IV)

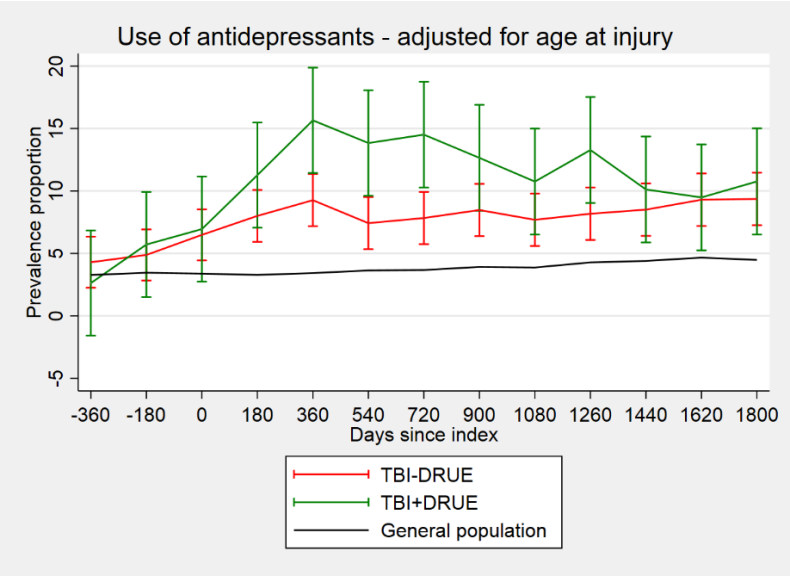

Figure 4.5.2: The prevalence proportion of dispensed antidepressants - adjusted for age at index in the TBI+DRUE and the TBI-DRUE subpopulations.
"0 days since index" corresponds to the period from index until 180 days post-index and so on. Adopted from Ryttersgaard et al. (Paper IV)

CHAPTER 5. DISCUSSION

5.1. DISCUSSION OF THE RESULTS

5.1.1. DEPRESSION AND COGNITIVE SEQUELAE

Depression

The systematic review verified that only few studies have reported on depression among adolescents and young adults (age 13-35-years) with moderate to severe TBI **(Paper I)**. The systematic review also showed that the prevalence proportion of depression and the quality of the studies varied a lot **(Paper I)**,[96] which corresponds with studies on the entire adult population.[30,31] Moreover, we demonstrated that the prevalence proportion of depression was higher among Danish adolescents and young adults with an intracranial traumatic lesion, examined less than a year after the injury **(Paper II)**.[99] Furthermore, we found a stable prevalence proportion of depression at the follow-up visit compared to the first visit among Danish adolescents and young adults who participated in the first interdisciplinary examination less than a year after injury **(Paper III)**. Finally, we showed that Danish adolescents and young adults with an intracranial traumatic lesion had a higher prevalence proportion of dispensed antidepressants from injury until 5 years post-injury compared to the general population **(Paper IV)**.

The high risk of depression seems to be in line with most of the existing literature on adolescents and young adults with moderate to severe TBI.[36,74,128–131] However, the prevalence proportion of depression only corresponded with the results from the study of Poggi et al. (2003),[131] as 5/7 of the included studies reported a higher prevalence proportion of depression,[36,74,128–130] and one study reported a very low prevalence proportion of depression.[127] Regarding prospective studies on adults with moderate to severe TBI, our results corresponded with the results from Alway et al.[27] while Hart et al. (2012) reported a higher prevalence proportion of depression 1- and 2 years post-injury.[35] The variation in the prevalence proportions could have different explanations: Firstly, the difference could be caused by the distinction in the diagnostic criteria for depression in ICD-10 and Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV). Secondly, the use of different assessment methods and as many of the existing studies report clinically significant depressive symptoms might also have an impact on the prevalence proportion.[31] Finally, DRUE contained information about traumatic diagnostic codes instead of GCS or PTA, which might have resulted in different study populations regarding the TBI severity.

The stable prevalence proportion of depression corresponds with the existing prospective studies on adolescents as well as on the entire adult population. O'Connor et al. (2012)[127] reported a stable but extremely low prevalence proportion of

depression (1.6%) among adolescents with moderate to severe TBI, while Alway et al. (2016)[27] and Hart et al. (2012)[35] reported a stable prevalence proportion of mood disorders/major depression disorder around 25% in the adult population. However, it must be considered that a stable prevalence proportion of depression in consecutive assessments in a study population might conceal individual differences. In our study, 7/11 patients who met the diagnostic criteria for depression at the first visit had remission of symptoms at the follow-up visit, while four new cases were identified at the follow-up visit (**Paper III**). This corresponds with the findings of Hart et al. (2012),[35] who found an overall stable prevalence proportion of depression from 1-year post-injury until 2 years post-injury, but 15.6% of the study population had remission of symptoms, while 13.6% who did not have depression at 1-year post-injury were classified as having a minor or major depression at 2 years post-injury.

The matched cohort study with long-term follow-up found a consistently higher prevalence proportion of dispensed antidepressant in the TBI-population from injury to 5-years post-injury compared to the general population matched controls **(Paper IV)**. The prevalence proportion in the TBI-population was more than two times as high compared to the general population matched controls from 6-months post-injury to 5-years post-injury. This corresponds to the findings of Viguier et al. (2001), although they found an even higher prevalence proportion of antidepressants (22.2%) in their population of young survivors with severe TBI.[133]

The high prevalence proportion of dispensed antidepressants could be in line with the existing literature regarding a high prevalence proportion of depression among young survivors of moderate to severe TBI. However, it must be considered that although antidepressants primarily are prescribed for treatment of clinical depression it can be prescribed for neurogenic pain, posttraumatic headache, anxiety and posttraumatic disorder.[134] Additionally, it should be considered that the young TBI-survivors had a higher prevalence proportion of dispensed antidepressant before the injury, which could imply that the young survivors of an intracranial traumatic lesion were more vulnerable than the general population even before the injury.

Our results support the existing literature regarding that depression can develop years after the injury.[31,35] This indicate that sequelae after TBI could be influenced by more than the biological changes in the brain,[37] and that psychosocial factors should be taken into account when evaluating and understanding outcome.[77,79] This means that sequelae after moderate to severe TBI are complex and that a biopsychosocial perspective (cf. section 1.3) is relevant in the understanding of depression after moderate to severe TBU, and that factors such as pre-injury psychiatric illness and how the young survivor cope/adapt to the new functional level could affect outcome.

Furthermore, the results indicate a need to have an ongoing focus on emotional sequelae in the clinical setting as depression e.g. can affect cognition,[59] outcome[99] and the effect of rehabilitation.[135] However, the complexity of sequelae after TBI and as

symptoms of direct sequelae from moderate to severe TBI do overlap with symptoms of depression, might complicate the identification of young TBI-survivors with depression.[37] The existing literature indicate a need to have a special focus on young TBI-survivors with pre-injury psychiatric disorder and limb-injury,[27,32,34] but due to the overlapping symptoms it could be relevant that health care professionals with expertise in acquired brain injury and psychiatric disorders are involved in the identification of young TBI-survivors with depression or in risk of developing depression.

Cognitive sequelae

We demonstrated that cognitive sequelae are frequent among young survivors of moderate to severe TBI **(Paper II+III)**, and that many of the young survivors have persistent cognitive sequelae **(Paper III).** The prevalence proportion of cognitive sequelae were stable from the first to the second visit (**Paper III**), but in section 4.3 we demonstrated that both clinical significant decline and improvement were detected on 7/8 of the neuropsychological tests at the follow-up visit compared to the performances at the first visit (cf. table 4.3).

Our results regarding that many of the young TBI survivors had persistent cognitive sequelae corresponds with the existing literature on children, adolescents and adults.[5,51,52,55] Although, adolescents and young adults might have an advantage regarding the extent of the cognitive difficulties when comparing with young children, our study determine that many adolescents and young adults struggle with cognitive sequelae after moderate to severe TBI. Our results seems to support, that persistent cognitive sequelae could affect the young TBI-survivors' possibilities to get a job and live an independent life, as we found that adolescents and young adults with depression and/or cognitive sequelae were less likely to have returned to work/school at the follow-up visit.

Changes in the cognitive functional level, with both improvement and deterioration on specific neuropsychological tests also corresponds with the existing literature.[53,57,58] The primary deterioration and improvement were found on neuropsychological tests that measure attention, processing speed as well as verbal learning and memory. We did not find any difference in the prevalence of positive change on the simple and complex attention task as presented by Marsh (2019).[53] This might indicate that adolescents and young adults could have improvement on complex attention later than 1-year post-injury. However, it must be considered that our study population was examined the first time less than a year post-injury and the second time approximately one-year after the first visit. Thus, the improvement on the complex attention test might be related to the spontaneous recovery.

Regarding deterioration, our study showed that cognitive decline could be detected as early as in the first 2 years post-injury. Due to the sample size, we could not investigate which factors that were related to the decline, but as presented in the introduction, adolescents and young adults with moderate to severe TBI could be in risk of growing into cognitive sequelae, as the TBI might affect the development of the brain.[5] However, the decline could also indicate that psychosocial factors, such as depression, could affect the performances on the neuropsychological tests, especially as deterioration was found on a neuropsychological test that measures simple attention and processing speed.[136]

The positive and negative changes on the performances on the neuropsychological tests support the understanding of sequelae after moderate to severe TBI as complex and it seems possible that the biopsychosocial factors could influence each other. Accordingly, cognitive difficulties might possibly both be direct and indirect sequelae after moderate to severe TBI.

5.1.2. NATIONAL STUDY ON YOUNG BRAIN INJURY SURVIVORS

The aim of the 'National study on young brain injury survivors' was to ensure that Danish adolescents and young adults with ABI had sufficient and timely rehabilitation so the young survivors could achieve the best possible outcome.

We demonstrated that almost 9/10 of the young TBI-survivors registered in DRUE participated in rehabilitation initiated by their municipality between the two visits at the outpatient clinics. Furthermore, we demonstrated that approximately 4/10 experienced an improvement in their global functional outcome **(Paper III)**. This might indicate that rehabilitation after discharge could have a positive impact on the global functional outcome among adolescents and young adults with moderate to severe TBI. This corresponds with the existing literature, as a review on community-based interventions for adolescents and young adults (age 11-25 years) concluded that although most of the existing studies had low methodological quality, the studies supported the hypothesis that community-based interventions after discharge improve outcome.[137] Furthermore, studies on adults have also shown that rehabilitation after discharge can improve outcome; León-Carrión et al. (2013) found that although rehabilitation in timely relation to the injury seemed most effective, rehabilitation more than 9 month after the injury did improve the global functional outcome,[138] Powell et al. (2002) found that multidisciplinary community-based rehabilitation even several years after severe TBI did improve social functioning[139] and Curran et al. (2015) found that continuing care including emotional support improved physical and psychosocial functioning[140] Unfortunately, the available data in DRUE did not enable us to investigate which rehabilitation initiatives that were most effective, and methodological limitations in studies on community-based interventions after

acquired brain injury make it difficult to establish evidence-based recommendations.[141]

The positive change in the global functional outcome could also be related to the time from injury to the first visit, as this was conducted less than a year post-injury, why spontaneous recovery could have had a positive impact on the global functional outcome (cf. Figure 1.1).[6] However, patients with cognitive sequelae and depression had a lower global functional outcome compared to the patients without cognitive sequelae and depression, which could indicate that both biological and psychosocial factors affect outcome. This means that other factors than the spontaneous recovery and rehabilitation might have had a positive impact on outcome. In studies of children, social factors, such as socio-economic status of the parents and family function has been identified as related to outcome.[5]

Our findings indicate that many of the young TBI survivors registered in DRUE struggled with returning to work/school and an association was detected between depression, cognitive sequelae and RTW **(Paper III)**. Only 59% of the young survivors who attended school/work-life before the injury had returned to work/school at the follow-up visit **(Paper III)**, which is lower than reported in previous studies on adolescents and young adults; Willmott et al. (2015) showed that among adolescents and young adults (age 13-34 years) with a complicated mild to severe TBI who were students prior to the injury 79.3% had returned to work/school 1-year post-injury.[74] Furthermore, Tibæk et al. (2019) reported a cumulative incidence of RTW at 85% 1-year post-injury among adolescents and young adults with skull fracture, multiple fractures of facial bones or intracranial traumatic lesion. However, Tibæk et al. (2019) also found that only 40-60% had a stable labour market attachment, which corresponds to our results.[88] However, it must be taken into account that both study populations varied from our study population, as Willmott et al. (2015) only included adolescents and young adults who were students prior to the injury,[74] and Tibæk et al. (2019) included patients with mild TBI without an intracranial traumatic lesion.[88] However, the fact that almost all the participants in our follow-up study **(Paper III)** received rehabilitation between the two visits could have postponed the RTW. On the other hand, the results in the one-year follow-up study **(Paper III)** correspond to studies on adults with moderate to severe TBI, as Ponsford et al. (2015)[142] found that 56-59% had returned to work 1-, 2- and 3-years post-injury, Grauwmeijer et al. (2012)[143] reported a RTW rate at 55% 3-years post-injury and Howe et al (2018)[18] found a relative stable employment probability around 50% 1-10 years post-injury. Even though the existing literature indicate that young survivors might have a more favourable outcome in relation to RTW compared to the whole adult population, we demonstrated that adolescents and young adults with moderate to severe TBI seems to resemble the whole adult population regarding return to work and school.

5.1.3. TBI+DRUE VS. TBI÷DRUE

Although the aim with DRUE was to ensure that all young ABI survivors was offered an interdisciplinary examination after discharge we demonstrated in **Paper IV** that only 1/5 of the possible young TBI-survivors were registered in DRUE and had an interdisciplinary examination as part of the national health initiative. However, interdisciplinary examination in the municipality or other outpatient clinics are not registered in a national register. Consequently, we do not know the exact number of young TBI-survivors who had their cognitive functional level, emotional state and need for rehabilitation assessed after discharge (**Paper IV**).

The TBI+DRUE and the TBI÷DRUE subpopulations resembled each other at time-of-injury regarding age, sex, highest education attained at injury and use of antidepressants in the year before the injury (**Paper IV)**. However, the distribution of TBI diagnostics codes differed between the two TBI subpopulations, primarily as more of the TBI÷DRUE had a diffuse traumatic brain injury or unspecified intracranial injury registered in NPR. Nevertheless, it seems not possible to conclude whether the TBI severity differed between the two subpopulations, as 21% of the TBI+DRUE subpopulation were identified in DRUE, as another diagnostic code were registered in NPR at injury.

The two TBI-subpopulations differed in the use of antidepressants during the period 1-year post-injury to 2.5-years post-injury when adjusting for age at injury **(Paper IV)**. This could imply that use of antidepressant was associated with participation in the national health initiative, however, an association can have several explanations. Firstly, the antidepressants could have been dispensed before the visit in the outpatient clinic and the depressive symptoms as well as the general practitioner (GP) might have motivated the young TBI-survivors to visit the outpatient clinic **(Paper IV)**. Secondly, the antidepressants could have been dispensed in relation to or after the visit. In such cases, the interdisciplinary examination might have revealed depressive symptoms that required treatment, or the initiated rehabilitation could have resulted in increased insight into the consequences of the TBI and consequently treatment with antidepressants were required **(Paper IV)**. The higher prevalence proportion of dispensed antidepressants might also indicate that patients referred to the outpatient clinics were more complex cases regarding psychosocial factors. However, the TBI+DRUE and the TBI÷DRUE subpopulations did not differ from each other regarding use of antidepressants pre-injury, which could indicate that the two subpopulations did not differ regarding pre-injury psychiatric disorder.

Although a difference in the prevalence proportion of dispensed antidepressants was determined between the two TBI-subpopulations, it must be considered that both subpopulations had a consistently higher prevalence proportion compared to the general population matched controls. This might indicate that young TBI-survivors are more vulnerable than the general population regarding development of depressive

symptoms, which corresponds with the existing literature on depression after TBI.[96,99] As presented in the introduction post-injury psychiatric disorder was associated with pre-injury psychiatric disorder, limb-injury and symptoms of anxiety and depression in the acute phase.[27,34,47] Furthermore, Cnossen et al. (2017) found that major depression disorder among adults with TBI were associated with pre-injury depression, female gender and post-injury job-loss. This indicate that pre-injury, injury- and post-injury related factors are associated with the development of depression.[144] The available data did not enable us to investigate whether this was the case regarding dispensing of antidepressants.

5.2. GENERAL METHODOLOGICAL ISSUES

5.2.1. SELECTION BIAS

In **Paper II-IV** we used ICD-10 diagnostic codes corresponding to an intracranial traumatic lesion as inclusion criteria (ICD-10 S06.1-S06.9). This was chosen as GCS or PTA were not registered in DRUE or NPR. Intracranial traumatic lesion corresponds to the continuum complicated mild TBI to severe TBI (cf. table 1.1), but the available data did not enable us to report on the distribution of TBI severities (complicated mild TBI, moderate TBI and severe TBI). This should be considered when comparing with other studies.

Only 1/5 of the young TBI-survivors were referred to the five outpatient clinics, which could result in selection bias. The low participation can have several reasons: Firstly, it can be due to lack of knowledge about the national health initiative, secondly, it can be because patients with none or few deficits were not referred, as they did not have an obvious need of rehabilitation and finally, it can be because patients with severe TBI were not referred, as their need of rehabilitation were obviously and initiated at discharge. The young TBI-survivors could be referred to the outpatient clinics from the hospital and GP. However, two of the five regions allowed referral from the municipality and another region contacted all relevant patients. The differences in referral possibilities might also result in selection bias.

In **Paper II** and **III** drop-out and missing data influenced the number of included patients and might result in selection bias, as it could be specific patients who wanted to participate in the interdisciplinary examination and the follow-up. However, the comparison of the included and excluded patients did not reveal any substantial differences.

The potential risk of selection bias was lower in **Paper IV** as the study included all adolescents and young adults who were 1) hospitalised at a Danish hospital in the study period, 2) registered in NPR or DRUE with one of the intracranial traumatic

lesion ICD-10 diagnostic codes and 3) had a highest education attained registered at injury. The risk of selection bias in the follow-up period were almost non existing, as follow-up based on the nationwide registries is very close to complete. Furthermore, we used a population-based control group generated by Statistics Denmark matched with replacement 1:10 on sex, age at injury and highest completed education at the time of injury.

5.2.2. INFORMATION BIAS

The method used to evaluate the prevalence proportion of depression and the definition of cognitive sequelae in **Paper II** and **III** might have resulted in information bias.

Studies of depression after traumatic brain injury report varying prevalence proportions, which is the case both in studies on adolescents and young adults **(Paper I)**[96] as well as in studies on the entire adult population.[30,31] Assessment method, pooling of TBI severities and different diagnostic criteria might affect the prevalence proportion, the comparability of studies as well as generalisability of the results.[31,145]

Paper II and III used the results from a self-report questionnaire, as this was the only available data in DRUE regarding depression. We tried to reduce the risk of information bias by using the ICD-10 diagnostic criteria for depression instead of the cut-off value. However this might have lowered the prevalence proportion of depression, as Sjöberg et al. (2017) showed that using ICD-10 diagnostic criteria resulted in a lower prevalence proportion compared to DSM-IV and self-report[145] and Nielsen et al. (2017) concluded that MDI is a conservative instrument for diagnosing depression that does not seem to over-diagnose depression in general practise[146]. Unfortunately, the data registered in DRUE did not make it possible to use the DSM-IV algorithm to investigate this further. Overall, the ICD-10 algorithm might have resulted in a conservative prevalence estimate, and the assessment method should be considered when comparing studies.

In **Paper II and III** we defined cognitive sequelae as *"a minimum of two performances 2 SD below the best available Danish population-based norms or non-completion due to cognitive difficulties"* (cf. section 3.3.2). This definition was chosen to avoid misinterpretation of one performance 2 SD below the mean being caused by the TBI[107] and to accommodate the fact that the young survivors' pre-injury level was not available. However, the definition might have increased the risk of underestimating the prevalence proportion of cognitive sequelae, as 43.4% (95% CI: 32.1-55.8) had at least one performance score that were ≥2 SD below the norm (**Paper III**). The definition of cognitive sequelae was made to identify whether young survivors of moderate to severe TBI have a higher risk of having a lower cognitive

functioning than the Danish general population of adolescents and young adults. However, it must be considered that we based the expected prevalence proportion in the healthy population on the Normal distribution, as the exact prevalence proportion of cognitive functioning equalling 2 performances 2 SD below the mean is not known.

Regarding the results of the neuropsychological test used in **Paper II and III** it must be considered that DRUE do not contain information about whether the neuropsychological test at the first and second visit were performed by the same neuropsychologist (rater) or whether the raters had the same introduction to the tests.

In **Paper IV** the risk of information bias seems very low, as the study is based on information from several registries with high validity, which reduces the risk of information bias.

5.2.3. CONFOUNDING

Paper II and **III** are observational studies that describe the prevalence of depression and cognitive sequelae among Danish adolescents and young adults with an intracranial traumatic lesion. The available data did not enable us to control for depression and cognitive level before the injury, however the existing literature made it possible to evaluate whether the prevalence proportions were higher than expected in the general population.

In **Paper IV** we tried to minimize the risk for confounding by including a matched control group so possible confounders, such as age, gender and highest education attained at injury were equally distributed in the TBI-population and the matched control group. However, the available data did not contain information on all possible confounders. Consequently, we could not adjust for variables such as pre-injury psychiatric disorder, length of hospitalisation and contacts to the GP. The length of hospitalisation could indicate the severity of the injury and many contacts to the GP might affect the possibility of having a prescription of antidepressants.

5.2.4. PRECISION

The study population in **Paper II** and **III** were relatively small with 96 and 76 included participants, respectively. The size of the study-populations resulted in wide 95% CIs, which might hide clinically relevant changes, differences, or associations. Consequently, due to the sample sizes caution are needed in relation to the risk of type 2 errors.

On the other hand, in **Paper IV** we benefitted from the fact that the Danish national registries made it possible to include all young TBI-survivors who were admitted to a Danish hospital in the period June 1, 2013 – October 31, 2016, had one of the including TBI diagnostic codes registered in NPR or DRUE and had a highest education attained registered at injury. Furthermore, the study benefitted from that all relevant data were linked due to the unique CPR number. This resulted in more narrow CIs, which reduced the risk that the study findings were influenced by chance.

5.2.5. EXTERNAL VALIDITY

This dissertation focuses on adolescents and young adults (age 15-30-years at injury) with moderate to severe TBI and the results might be restricted to this age-group. Furthermore, as **Paper II** and **III** are based on a national health initiative and only 1/5 of the TBI-population were referred to one of the five outpatient clinics might further restrict the generalisability of the results.

Paper IV included all Danish adolescents and young adults who were admitted to a Danish Hospital in the period June 1, 2013, until October 31, 2016, and had an intracranial traumatic diagnostic code registered in NPR or DRUE and it seems fair to conclude that the results can be generalised to countries with a well-developed hospital system.

CHAPTER 6. CONCLUSION, FUTURE RESEARCH AND CLINICAL IMPLICATIONS

6.1. CONCLUSION

Knowledge on depression and cognitive sequelae among adolescents and young adults with moderate to severe TBI are sparse, but our results indicate that depression and cognitive sequelae are frequent among young survivors of moderate to severe TBI. This is worrying as our results also indicate that young TBI-survivors with depression and/or cognitive sequelae have a lower global functional outcome and difficulties with return to work/school. Furthermore, our results indicate that young survivors of moderate to severe TBI could be more vulnerable than the general population, as they have a continuously higher use of antidepressants from injury to 5 years post-injury compared to the general population.

Furthermore, the results indicate that depression, cognitive sequelae, and outcome are dynamic factors with positive and negative changes even years after the injury. This could be related to the fact that TBI in adolescence and young adulthood might influence the ongoing development of the brain, and that the young TBI-survivors might be in risk of growing into difficulties, as the demands in their everyday life changes. However, the results could also indicate that both direct and indirect sequelae affect outcome, and that biological as well as psychosocial factors should be considered when evaluating outcome and planning rehabilitation.

Taken together the results indicate that young survivors of moderate to severe TBI are more vulnerable than their age-matched peers even years after the injury. Consequently, it seems important to identify young TBI-survivors with cognitive and emotional sequelae immediately after the injury to ensure that they receive rehabilitation and support in relation to return to work/school. However, as emotional sequelae could develop months or years after the injury and psychosocial factors seems to influence outcome could indicate a need for follow-up after discharge. The fact that symptoms of depression do overlap with other sequelae of TBI, such as fatigue, concentrations difficulties and sleep problems might influence the identification of post-TBI depression, which could call for a follow-up by specialists in acquired brain injury and psychiatry.

6.2. FUTURE RESEARCH AND CLINICAL IMPLICATIONS

Based on the results of this thesis it seems relevant to get more knowledge about sequelae and outcome among adolescents and young adults with moderate to severe TBI to understand long-term outcome and to improve the identification of young TBI-survivors in risk of depression.

As a moderate to severe TBI in adolescence and young adulthood affect the developing brain, it seems relevant to get more knowledge about whether the pathophysiological changes in the brain affect the ongoing development. This knowledge will give insight into whether young TBI-survivors are in risk of growing into cognitive difficulties as the demands in their daily life increase. Furthermore, it seems relevant to investigate which factors that are related to return to work/school. This to ensure inclusion in the educational system and the labour market.

As symptoms of post-TBI depression can overlap with other sequelae of TBI, which might complicate diagnosing of depression, it seems important to investigate whether self-report questionnaires, such as MDI can be used for diagnosing depression after moderate to severe TBI. Furthermore, it seems relevant to get more knowledge about risk factors for post-TBI depression, as this could help health professionals in the acute phase and GPs in the identification of young TBI-survivors in risk of developing post-TBI depression.

Likewise, it seems important to investigate the effect of antidepressants among young TBI-survivors, as our results indicate that the young TBI-survivors have a continuously higher use of antidepressant until 5 years post-injury compared to the general population. In general, it seems relevant to get more knowledge about, which treatments that are most effective for adolescents and young adults: pharmacological, non-pharmacological or a combination of both.

The thesis indicate that the biopsychosocial perspective is relevant in the understanding of the complexity of sequelae after TBI. The biopsychosocial model and the ICF framework do illustrate how biological, psychological, and social factors affect participation, activity, and the understanding of the TBI. Implementation of the models in the communication with the young TBI-survivors and their relatives might help to illustrate how other factors than the brain injury affect participation and activity, but could also be used to understand which daily life activities that are most important for the young TBI-survivor.

Identification of young TBI-survivors in risk of cognitive and emotional sequelae might require ongoing education of healthcare professionals at the hospitals, GPs and relevant employees in the municipalities. Ongoing education could be done by developing an e-learning programme that in few minutes inform about cognitive and emotional sequelae among young TBI-survivors, interdisciplinary examination after

discharge and rehabilitation. It seems relevant to include young TBI-survivors and healthcare professionals in the development of such an e-learning programme.

REFERENCES

1. Johnson WD, Griswold DP. Traumatic brain injury: a global challenge. *Lancet Neurol*. 2017;16(12):949-950. doi:10.1016/S1474-4422(17)30362-9

2. James SL, Bannick MS, Montjoy-Venning WC, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):56-87. doi:10.1016/S1474-4422(18)30415-0

3. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)*. 2015;157(10):1683-1696. doi:10.1007/s00701-015-2512-7

4. Norup A, Kruse M, Soendergaard PL, Rasmussen KW, Biering-Sørensen F. Socioeconomic Consequences of Traumatic Brain Injury: A Danish Nationwide Register-Based Study. *J Neurotrauma*. 2020;9:1-9. doi:10.1089/neu.2020.7064

5. Crowe LM, Catroppa C, Anderson V. Sequelae in children: developmental concequences. In: Grafman J, Salazar AM, eds. *Handbook of Clinical Neurology*. Vol. 128. Elsevier B.V.; 2015:661-677.

6. Cristofori I, Levin HS. Traumatic brain injury and cognition. In: Grafman J, Salazar AM, eds. *Handbook of Clinical Neurology*. Vol. 128. Elsevier B.V.; 2015:579-611.

7. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: Definition of traumatic brain injury. *Arch Phys Med Rehabil*. 2010;91(11):1637-1640. doi:10.1016/j.apmr.2010.05.017

8. Wortzel HS, Arciniegas DB. The DSM-5 approach to the evaluation of traumatic brain injury and its neuropsychiatric sequelae. *NeuroRehabilitation*. 2014;34(4):613-623. doi:10.3233/NRE-141086

9. Hawryluk GWJ, Manley GT. Classification of traumatic brain injury: past, present and future. In: Grafman J, Salazar AM, eds. *Handbook of Clinical Neurology*. Elsevier B.V.; 2015:15-21.

10. Mckee AC, Daneshvar DH. *The Neuropathology of Traumatic Brain Injury*. Vol 127. (Grafman J, Salazar AM, eds.). Elsevier B.V.; 2015. doi:10.1016/B978-0-444-52892-6.00004-0.The

11. Mateu NC. Traumatic brain injury in Denmark 2008–2012. *Scand J Public Health*. 2020;48(3):331-337. doi:10.1177/1403494819852826

12. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet Neurol*. 1974;304(7872):81-84.

13. Kashluba S, Hanks RA, Casey JE, Millis SR. Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Arch Phys Med Rehabil*. 2008;89(5):904-911. doi:10.1016/j.apmr.2007.12.029

14. Williams DH, Levin HS, Eisenberg HM. Mild Head Injury Classification. *Neurosurgery*. 1990;27(3):422-428.

15. Kay T, Harrington DE, Adams R. American Congress of Rehabilitation Medicine, Head Injury Interdisciplinary Special Interest Group. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993;8(3):86-87. https://www.acrm.org/wp-content/uploads/pdf/TBIDef_English_10-10.pdf%0Apapers2://publication/uuid/1E91D994-F6EB-44E6-9508-05A5E2A870D6

16. Stein SC. Minor head injury: 13 is an unlucky number. *J Trauma - Inj Infect Crit Care*. 2001;50(4):759-760. doi:10.1097/00005373-200104000-00032

17. Undén J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. *BMC Med*. 2013;11(1):50. doi:10.1186/1741-7015-11-50

18. Howe EI, Andelic N, Perrin PB, et al. Employment probability trajectories up to 10 years after moderate-to-severe traumatic brain injury. *Front Neurol*. 2018;9(December):1-10. doi:10.3389/fneur.2018.01051

19. Forslund M V., Arango-Lasprilla JC, Roe C, Perrin PB, Sigurdardottir S, Andelic N. Multi-level modelling of employment probability trajectories and employment stability at 1, 2 and 5 years after traumatic brain injury. *Brain Inj*. 2014;28(7):980-986. doi:10.3109/02699052.2014.888770

20. Perrin PB, Niemeier JP, Mougeot JL, et al. Measures of injury severity and prediction of acute traumatic brain injury outcomes. *J Head Trauma Rehabil*. 2015;30(2):136-142. doi:10.1097/HTR.0000000000000026

21. Ponsford J, Draper K, Schönberger M. Functional outcome 10 years after traumatic brain injury: Its relationship with demographic, injury severity, and cognitive and emotional status. *J Int Neuropsychol Soc*. 2008;14(2):233-242. doi:10.1017/S1355617708080272

22. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. Published online 2018:1-18. doi:10.3171/2017.10.JNS17352

23. Engberg AW, Teasdale TW. Traumatic brain injury in Denmark 1979-1996. A national study of incidence and mortality. *Eur J Epidemiol*. 2001;17(5):437-442. doi:10.1023/A:1013733107520

24. Tibæk M, Forchhammer HB, Dehlendorff C, Johnsen SP, Kammersgaard LP. Incidence and mortality of acquired brain injury in young Danish adults between 1994 and 2013: a nationwide study. *Brain Inj*. 2017;31(11):1455-1462. doi:10.1080/02699052.2017.1376757

25. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B. The economic cost of brain disorders in Europe. *Eur J Neurol*. 2012;19(1):155-162. doi:10.1111/j.1468-1331.2011.03590.x

26. Whelan-Goodinson R, Ponsford J, Johnston L, Grant F. Psychiatric disorders following traumatic brain injury: Their nature and frequency. *J Head Trauma Rehabil*. 2009;24(5):324-332. doi:10.1097/HTR.0b013e3181a712aa

27. Alway Y, Gould KR, Johnston L, McKenzie D, Ponsford J. A prospective examination of Axis I psychiatric disorders in the first 5 years following moderate to severe traumatic brain injury. *Psychol Med*. 2016;46(6):1331-1341. doi:10.1017/S0033291715002986

28. Gould KR, Ponsford JL, Johnston L, Schönberger M. The nature, frequency and course of psychiatric disorders in the first year after traumatic brain injury: A prospective study. *Psychol Med*. Published online 2011. doi:10.1017/S003329171100033X

29. Ponsford J, Alway Y, Gould K. Epidemiology and natural history of psychiatric disorders after TBI. *J Neuropsychiatry Clin Neurosci*. 2018;30(4):262-270.

30. Scholten AC, Haagsma JA, Cnossen MC, Olff M, van Beeck EF, Polinder S. Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: A systematic review. *J Neurotrauma*. 2016;33(22):1969-1994. doi:10.1089/neu.2015.4252

31. Osborn AJ, Mathias JL, Fairweather-Schmidt AK. Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neurosci Biobehav Rev*. 2014;47:1-15. doi:10.1016/j.neubiorev.2014.07.007

32. Laliberté Durish C, Pereverseff RS, Yeates KO. Depression and depressive symptoms in pediatric traumatic brain injury. *J Head Trauma Rehabil*. 2017;33(3):E18-E30. doi:10.1097/HTR.0000000000000343

33. Iljazi A, Ashina H, Al-Khazali HM, Ashina M, Winther Schytz H, Ashina S. Post-traumatic stress disorder attributed to traumatic brain injury in children–a systematic review. *Brain Inj*. 2020;34(7):857-863. doi:10.1080/02699052.2020.1764104

34. Arif H, Troyer EA, Paulsen JS, et al. Long-Term Psychiatric Outcomes in Adults with History of Pediatric Traumatic Brain Injury. *J Neurotrauma*. 2021;38(11):1515-1525. doi:10.1089/neu.2020.7238

35. Hart T, Hoffman JM, Pretz C, Kennedy R, Clark AN, Brenner LA. A longitudinal study of major and minor depression following traumatic brain injury. *Arch Phys Med Rehabil*. 2012;93(8):1343-1349. doi:10.1016/j.apmr.2012.03.036

36. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA*. 2010;303(19):1938-1945.

37. Juengst SB, Kumar RG, Wagner AK. A narrative literature review of depression following traumatic brain injury: Prevalence, impact, and management challenges. *Psychol Res Behav Manag*. 2017;10:175-186. doi:10.2147/PRBM.S113264

38. Juengst SB, Kumar RG, Failla MD, et al. Acute Inflammatory Biomarker Profiles Predict Depression Risk Following Moderate to Severe Traumatic Brain Injury. *J Head Trauma Rehabil*. 30(3):207-218. doi:10.1097/HTR.0000000000000031

39. Spitz G, Alway Y, Gould KR, Ponsford JL. Disrupted White Matter Microstructure and Mood Disorders after Traumatic Brain Injury. *J Neurotrauma*. 2017;34(4):807-815. doi:10.1089/neu.2016.4527

40. Klyce DW, Stromberg KA, Walker WC, et al. Depression as a Predictor of Long-term Employment Outcomes Among Individuals With Moderate-to-Severe Traumatic Brain Injury. *Arch Phys Med Rehabil*. 2019;100(10):1837-1843. doi:10.1016/j.apmr.2019.06.009

41. DiSanto D, Kumar RG, Juengst SB, et al. Employment Stability in the First 5 Years After Moderate-to-Severe Traumatic Brain Injury. *Arch Phys Med Rehabil*. 2019;100(3). doi:10.1016/j.apmr.2018.06.022

42. Hart T, Brenner L, Clark AN, et al. Major and minor depression after traumatic brain injury. *Arch Phys Med Rehabil*. 2011;92(8):1211-1219. doi:10.1016/j.apmr.2011.03.005

43. Hart T, Fann JR, Chervoneva I, et al. Prevalence, Risk Factors, and Correlates of Anxiety at 1 Year after Moderate to Severe Traumatic Brain Injury. *Arch Phys Med Rehabil*. 2016;97(5):701-707. doi:10.1016/j.apmr.2015.08.436

44. Erler KS, Kew CL, Juengst SB. Participation differences by age and depression 5 years after moderate-to-severe traumatic brain injury. *Int Rev Psychiatry*. 2020;32(1):12-21. doi:10.1080/09540261.2019.1656175

45. Underhill AT, Lobello SG, Stroud TP, Terry KS, Devivo MJ, Fine PR. Depression and life satisfaction in patients with traumatic brain injury: A longitudinal study. *Brain Inj*. 2003;17(11):973-982. doi:10.1080/0269905031000110418

46. O'Neil-Pirozzi TM, Pinto SM, Sevigny M, Hammond FM, Juengst SB, Bombardier CH. Factors Associated With High and Low Life Satisfaction 10 Years After Traumatic Brain Injury. *Arch Phys Med Rehabil*. Published online 2022. doi:10.1016/j.apmr.2022.01.159

47. Gould K., Ponsford J, Johnston L, Schönberger M. Predictive and associated factors of psychiatric disorders after traumatic brain injury: A prospective study. *J Neurotrauma*. 2011;28(7):1155-1163. doi:10.1089/neu.2010.1528

48. Seel RT, MacCiocchi S, Kreutzer JS. Clinical considerations for the diagnosis of major depression after moderate to severe tBI. *J Head Trauma Rehabil*. 2010;25(2):99-112. doi:10.1097/HTR.0b013e3181ce3966

49. McCullagh S, Feinstein A. Cognitive changes. In: Silver JM, McAlliste TW, Yudofsky SC, eds. *Textbook of Traumatic Brain Injury*. 1st ed. American Psychiatric Publishing; 2005:321-336.

50. Novack TA, Alderson AL, Bush BA, Meythaler JM, Canupp K. Cognitive and functional recovery at 6 and 12 months post-TBI. *Brain Inj*. 2000;14(11):987-996. doi:10.1080/02699050050191922

51. Dikmen SS, Corrigan JD, Levin HS, MacHamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):430-438. doi:10.1097/HTR.0b013e3181c133e9

52. Griffen J, Hanks R. Cognitive and behavioral outcomes from traumatic brain injury. In: Sherer M, Sander AM, eds. *Handbook on the Neuropyschology of Traumatic Brain Injury, Clinical Handbooks in Neuropsychology*. 1st ed. Springer-Verlag; 2014:25-45.

53. Marsh N. Cognitive functioning following traumatic brain injury: The first 5 years. *NeuroRehabilitation*. 2019;43(4):377-386. doi:10.3233/NRE-182457

54. Lannoo E, Colardyn F, Jannes C, de Soete G. Course of neuropsychological recovery from moderate-to-severe head injury: a 2-year follow-up. *Brain Inj*. 2001;15(1):1-13. doi:10.1080/02699050121191

55. Stålnacke BM, Saveman BI, Stenberg M. Long-term follow-up of disability, cognitive, and emotional impairments after severe traumatic brain injury. *Behav Neurol*. 2019;2019. doi:10.1155/2019/9216931

56. Forslund M V., Roe C, Sigurdardottir S, Andelic N. Predicting health-related quality of life 2 years after moderate-to-severe traumatic brain injury. *Acta Neurol Scand*. 2013;128(4):220-227. doi:10.1111/ane.12130

57. Millis SR, Rosenthal M, Novack TA, et al. Long-term neuropsychological outcome after traumatic brain injury. *J Head Trauma Rehabil*. 2001;16(4):343-355. doi:10.1097/00001199-200108000-00005

58. Till C, Colella B, Verwegen J, Green RE. Postrecovery Cognitive Decline in Adults With Traumatic Brain Injury. *Arch Phys Med Rehabil*. 2008;89(12 SUPPL.):S25-S34. doi:10.1016/j.apmr.2008.07.004

59. Knight MJ, Baune BT. Cognitive dysfunction in major depressive disorder. *Curr Opin Psychiatry*. 2018;31(1):26-31. doi:10.1097/YCO.0000000000000378

60. Stenberg M, Godbolt AK, Nygren De Boussard C, Levi R, Stålnacke BM. Cognitive impairment after severe traumatic brain injury, clinical course and impact on outcome: A Swedish-icelandic study. *Behav Neurol*. 2015;2015:680308. doi:10.1155/2015/680308

61. Anderson V, Moore C. Age at Injury as a Predictor of Outcome Following Pediatric Head Injury: A Longitudinal Perspective. *Child Neuropsychol*. 1995;1(3):187-202. doi:10.1080/09297049508400224

62. Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the Functional Independence Measure. *Arch Phys Med Rehabil*. 1994;75(2):127-132.

63. Rappaport M, Cope DN. Disability rating scale for severe head trauma: coma to community. *Arch Phys Med Rehabil*. 1982;63:118-123.

64. Honan CA, McDonald S, Tate R, et al. Outcome instruments in moderate-to-severe adult traumatic brain injury: recommendations for use in psychosocial research. *Neuropsychol Rehabil*. 2019;29(6):896-916. doi:10.1080/09602011.2017.1339616

65. Sigurdardottir S, Andelic N, Roe C, Schanke AK. Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. *J Int Neuropsychol Soc*. 2009;15(5):740-750. doi:10.1017/S1355617709990452

66. Sandhaug M, Andelic N, Langhammer B, Mygland A. Functional level during the first 2 years after moderate and severe traumatic brain injury. *Brain Inj*. 2015;29(12):1431-1438. doi:10.3109/02699052.2015.1063692

67. McCrea MA, Giacino JT, Barber J, et al. Functional Outcomes over the First Year after Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study. *JAMA Neurol*. 2021;78(8):982-992. doi:10.1001/jamaneurol.2021.2043

68. Forslund M V., Perrin PB, Røe C, et al. Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. *Front Neurol*. 2019;10(March). doi:10.3389/fneur.2019.00219

69. McMillan TM, Teasdale GM, Stewart E. Disability in young people and adults after head injury: 12-14 Year follow-up of a prospective cohort. *J Neurol Neurosurg Psychiatry*. 2012;83(11):1086-1091. doi:10.1136/jnnp-2012-302746

70. Whitnall L, McMillan TM, Murray GD, Teasdale GM. Disability in young people and adults after head injury: 5-7 Year follow up of a prospective cohort study. *J Neurol Neurosurg Psychiatry*. 2006;77(5):640-645. doi:10.1136/jnnp.2005.078246

71. Corrigan JD, Cuthbert JP, Harrison-Felix C, et al. US population estimates of health and social outcomes 5 years after rehabilitation for traumatic brain injury. *J Head Trauma Rehabil*. 2014;29(6):E1-E9. doi:10.1097/HTR.0000000000000020

72. Forslund M V., Roe C, Perrin PB, et al. The trajectories of overall disability in the first 5 years after moderate and severe traumatic brain injury. *Brain Inj*. 2017;31(3):329-335. doi:10.1080/02699052.2016.1255778

73. Ponsford JL, Downing MG, Olver J, et al. Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *J Neurotrauma*. 2014;31(1):64-77. doi:10.1089/neu.2013.2997

74. Willmott C, Spitz G, Ponsford JL. Predictors of productivity outcomes for secondary and tertiary students following traumatic brain injury. *Brain Inj*. 2015;29(7-8):929-936. doi:10.3109/02699052.2015.1022882

75. Tanaka C, Matsui M, Uematsu A, Noguchi K, Miyawaki T. Developmental trajectories of the fronto-temporal lobes from infancy to early adulthood in healthy individuals. *Dev Neurosci*. 2013;34(6):477-487. doi:10.1159/000345152

76. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004;101(21):8174-8179. doi:10.1073/pnas.0402680101

77. Engel GL. The Need for a New Medical Model : A Challenge for Biomedicine Author (s): George L . Engel. *Am Assoc Adv Sci*. 1977;196(4286):129-136.

78. Üstün TB, Chatterji S, Bickenbach J, Kostanjsek N, Schneider M. The International Classification of Functioning, Disability and Health: A new tool for understanding disability and health. *Disabil Rehabil*. 2003;25(11-12):565-571. doi:10.1080/0963828031000137063

79. World Health Organisation. *Towards a Common Language for Functioning, Disability and Health: ICF.*; 2002. http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf

80. World Health Organisation. International Classification of Functioning, Disability and Health (ICF). Accessed November 3, 2022. https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health

81. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. *Lancet Child Adolesc Heal*. 2018;2(3):223-228. doi:10.1016/S2352-4642(18)30022-1

82. Coleman JC. *The Nature of Adolescence*. 4th ed. Routledge; 2011.

83. Kakonge L, Charron VP, Vedder J, Wormald K, Turkstra LS. A mapping review of adolescent identity after TBI: what clinicians need to know. *Neuropsychol Rehabil*. 2022;(May):1-36. doi:10.1080/09602011.2022.2071299

84. Sirois K, Tousignant B, Boucher N, et al. The contribution of social cognition in predicting social participation following moderate and severe TBI in youth. *Neuropsychol Rehabil*. 2019;29(9):1383-1398. doi:10.1080/09602011.2017.1413987

85. De Kloet AJ, Gijzen R, Braga LW, Meesters JJL, Schoones JW, Vliet Vlieland TPM. Determinants of participation of youth with acquired brain injury: A systematic review. *Brain Inj*. 2015;29(10):1135-1145. doi:10.3109/02699052.2015.1034178

86. Doser K, Poulsen I, Wuensch A, Norup A. Psychological outcome after severe traumatic brain injury in adolescents and young adults: The chronic phase. *Brain Inj*. 2018;32(1):64-71. doi:10.1080/02699052.2017.1363408

87. Di Battista A, Godfrey C, Soo C, Catroppa C, Anderson V. Depression and health related quality of life in adolescent survivors of a traumatic brain injury: A pilot study. *PLoS One*. 2014;9(7):e101842. doi:10.1371/journal.pone.0101842

88. Tibæk M, Kammersgaard LP, Johnsen SP, Dehlendorff C, Forchhammer HB. Long-term return to work after acquired brain injury in young danish adults: A nation-wide registry-based cohort study. *Front Neurol*. 2019;9:1-9. doi:10.3389/fneur.2018.01180

89. Max JE, Wilde EA, Bigler ED, et al. Psychiatric Disorders After Pediatric Traumatic Brain Injury: A Prospective, Longitudinal, Controlled Study. *J Neuropsychiatry Clin Neurosci*. 2012;24(4):427-436. doi:10.1176/appi.neuropsych.12060149

90. Moran LM, Babikian T, Del Piero L, et al. The UCLA study of predictors of cognitive functioning following moderate/severe pediatric traumatic brain injury. *J Int Neuropsychol Soc*. 2016;22(5):512-519. doi:10.1017/S1355617716000175

91. Catroppa C, Godfrey C, Rosenfeld J V., Hearps SSJC, Anderson VA. Functional recovery ten years after pediatric traumatic brain injury: Outcomes and predictors. *J Neurotrauma*. 2012;29(16):2539-2547. doi:10.1089/neu.2012.2403

92. Ponsford J, Harrison-Felix C, Ketchum JM, Spitz G, Miller AC, Corrigan JD. Outcomes 1 and 2 Years After Moderate to Severe Traumatic Brain Injury: An International Comparative Study. *Arch Phys Med Rehabil*. 2021;102(3):371-377. doi:10.1016/j.apmr.2020.09.387

93. Sigurdardottir S, Andelic N, Roe C, Schanke AK. Identifying longitudinal trajectories of emotional distress symptoms 5 years after traumatic brain injury. *Brain Inj*. 2014;28(12):1542-1550. doi:10.3109/02699052.2014.934285

94. Sundhedsstyrelsen. *Slutevaluering Af Styrket Indsats Til Unge Med Erhvervet Hjerneskade [In English: Evaluation of the National Study on Young Brain Injury Survivors]*.; 2018.

95. Svendsen SW, Ingeman A. *Dansk Register for Unge Med Erhvervet Hjerneskade - DRUE. Baggrund Og Dataoversigt. [Danish Registry for Young Adults with Aquired Brain Injury - DRUE. Background and Summary of Data*.; 2017.

96. Ryttersgaard TO, Johnsen SP, Riis JØ, Mogensen PH, Bjarkam CR. Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review. *Scand J Psychol*. 2020;61(2):297-306. doi:10.1111/sjop.12587

97. Andriessen TMJC, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *J Cell Mol Med*. 2010;14(10):2381-2392. doi:10.1111/j.1582-4934.2010.01164.x

98. *ICD-10 : International Statistical Classification of Diseases and Related Health Problems*. 2016th ed. World Health Organization; 2016.

99. Ryttersgaard TO, Riis JØ, Johnsen SP, Mogensen PH, Bjarkam CR. Depression and cognitive sequelae registered within the first year among young Danish TBI survivors. *Scand J Psychol*. 2020;61(5):663-670. doi:10.1111/sjop.12660

100. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39(7):30-33. doi:10.1177/1403494811401482

101. Statistics Denmark. *Uddannelsesstatistikkens Manual*.; 2020. https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=uddannelse&fo=uddannelsesmanual--pdf&ext=%7B2%7D (Last accessed March 2022)

102. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012. doi:10.1016/j.jclinepi.2009.06.005

103. Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord*. 2001;66(2-3):159-164. Accessed January 16, 2019. http://www.ncbi.nlm.nih.gov/pubmed/11578668

104. Bech P, Timmerby N, Martiny K, Lunde M, Soendergaard S. Psychometric evaluation of the Major Depression Inventory (MDI) as depression severity scale using the LEAD (Longitudinal Expert Assessment of All Data) as index of validity. *BMC Psychiatry*. 2015;15(1):1-7. doi:10.1186/s12888-015-0529-3

105. Olsen L, Jensen D, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychol Med*. 2003;33(2):351-356. Accessed January 16, 2019. http://www.ncbi.nlm.nih.gov/pubmed/12622314

106. Svendsen S., Ingeman A, Ryttersgaard T., Frandsen MW. *Dansk Register for Unge Med Erhvervet Hjerneskade DRUE - Datadefinitioner for Fagpersonskema 1. Besøg [Danish Registry for Young Adults with Aquired Brain Injury DRUE - Definition of Data in Professionel Scheme at the First Visit]*.; 2017.

107. Binder LM, Iverson GL, Brooks BL. To err is human: "abnormal" Neuropsychological scores and variability are common in healthy adults. *Arch Clin Neuropsychol*. 2009;24(1):31-46. doi:10.1093/arclin/acn001

108. Reitan R. *Trail Making Test. Manual for Administration and Scoring*. Reitan Neuropsychology Laboratory; 1992.

109. Buschke H, Fuld P. Evaluating storage, retention and retrieval in disordered memory and learning. *Neurology*. 1974;24:1019-1025.

110. Strauss E, Sherman E, Spreen O. *A Compendium of Neuropsychological Tests. Administration, Norms and Commentary*. 3ed ed. Oxford University Press; 2006.

111. Wechsler D. *Wechsler Adult Intelligance Scale - Fourth Edition, WAIS-IV Danish Version*. Pearson Assessment; 2011.

112. Jørgensen K. *Danske Normer Til Neuropsykologiske Tests*. Dansk Psykologisk Forlag A/S; 2012.

113. Hudak AM, Caesar RR, Frol AB, et al. Functional outcome scales in traumatic brain injury: A comparison of the Glasgow Outcome Scale (extended) and the functional status examination. *J Neurotrauma*. 2005;22(11):1319-1326. doi:10.1089/neu.2005.22.1319

114. Wilson JTL, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for their use. *J Neurotrauma*. 1998;15(8):573-585. doi:10.1089/neu.1998.15.573

115. Svendsen SW, Ingeman A. *Dansk Register for Unge Med Erhvervet Hjerneskade DRUE - Datadefintioner for Fagpersonskema Kontrol 1 År [In English: DRUE - Definition of Data in Professional Scheme at One Year Follow-Up]*.; 2017.

116. Svendsen SW, Ingeman A. *Dansk Register for Unge Med Erhvervet Hjerneskade DRUE - Datadefintioner for Patientskema Kontrol 1 År [In English: DRUE - Definition of Data in Self-Report Questionnaire at One Year Follow-Up]*.; 2017.

117. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

118. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

119. Kildemoes HW, Toft Sørensen H, Hallas J. The Danish national prescription registry. *Scand J Public Health*. 2011;39(7):38-41. doi:10.1177/1403494810394717

120. Statistics Denmark. *Documentation of Statistics for The Population*.; 2020. https://www.dst.dk/Site/Dst/SingleFiles/GetArchiveFile.aspx?fi=98812100280&fo=0&ext=kvaldel (Last accessed March 2022)

121. Viswanathan M, Ansari M, Berkman N, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In: *Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews*. Agency for Healthcare Research and Quality.; 2014:1-33. doi:22479713

122. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration. Available from http://handbook.cochrane.org.; 2011.

123. Dikmen SS, Machamer JE, Winn HR, Temkin NR. Neuropsychological Outcome at 1-Year Post Head Injury. *Neuropsychology*. 1995;9(1):80-90. doi:10.1037/0894-4105.9.1.80

124. StataCorp. Stata Statistical Software: Release 15. Published online 2017.

125. StataCorp. Stata Statistical Software: Release 16. Published online 2019.

126. StataCorp. Stata Statistical Software: Release 17. Published online 2021.

127. O'Connor SS, Zatzick DF, Wang J, et al. Association between posttraumatic stress, depression, and functional impairments in adolescents 24 months after traumatic brain injury. *J Trauma Stress*. 2012;25(3):264-271. doi:10.1002/jts.21704

128. Tyerman A, Humphrey M. Changes in self-concept following severe head injury. *Int J Rehabil Res*. 1984;7(1):11-23.

129. van Reekum R, Bolago I, Finlayson MAJ, Garner S, Links PS. Psychiatric disorders after traumatic brain injury. *Brain Inj*. 1996;10(5):319-328. doi:10.1080/026990596124340

130. Garske GG, Thomas KR. Self-reported self-esteem and depression: Indexes of psychological adjustment following severe traumatic brain injury. *Rehabil Couns Bull*. 1992;36(1):44-52.

131. Poggi G, Liscio M, Adduci A, et al. Neuropsychiatric sequelae in TBI: A comparison across different age groups. *Brain Inj*. 2003;17(10):835-846. doi:10.1080/0269905031000088612

132. Bombardier CH, Hoekstra T, Dikmen S, Fann JR. Depression trajectories during the first year after traumatic brain injury. *J Neurotrauma*. 2016;33:2115-2124. doi:10.1089/neu.2015.4349

133. Viguier D, Dellatolas G, Gasquet I, Martin C, Choquet M. A psychological assessment of adolescent and young adult inpatients after traumatic brain injury. *Brain Inj*. 2001;15(3):263-271. doi:10.1080/026990501300005703

134. Retsinformation. *Vejledning Om Behandling Af Voksne Med Antidepressive Lægemidler [In English: Instruction on Treatment with Antidepressant Medication to Adults]*.; 2014.

135. Lewis FD, Horn GJ. Depression following traumatic brain injury: Impact on post-hospital residential rehabilitation outcomes. *NeuroRehabilitation*. 2017;40(3):401-410. doi:10.3233/NRE-161427

136. Perini G, Ramusino MC, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: Recent advances and novel treatments. *Neuropsychiatr Dis Treat*. 2019;15:1249-1258. doi:10.2147/NDT.S199746

137. Clasby B, Hughes N, Catroppa C, Morrison E. Community-based interventions for adolescents following traumatic brain injury: A systematic review. *NeuroRehabilitation*. 2018;42(3):345-363. doi:10.3233/NRE-172385

138. León-Carrión J, MacHuca-Murga F, Solís-Marcos I, León-Domínguez U, Domínguez-Morales MDR. The sooner patients begin neurorehabilitation, the better their functional outcome. *Brain Inj*. 2013;27(10):1119-1123. doi:10.3109/02699052.2013.804204

139. Powell J, Heslin J, Greenwood R. Community based rehabilitation after severe traumatic brain injury: A randomised controlled trial. *J Neurol Neurosurg Psychiatry*. 2002;72(2):193-202. doi:10.1136/jnnp.72.2.193

140. Curran C, Dorstyn D, Polychronis C, Denson L. Functional outcomes of community-based brain injury rehabilitation clients. *Brain Inj*. 2015;29(1):25-32. doi:10.3109/02699052.2014.948067

141. Hauger SL, Borgen IMH, Løvstad M, et al. Community-Based Interventions After Acquired Brain Injury—A Systematic Review of Intervention Types and Their Effectiveness. *J Head Trauma Rehabil*. 2022;Publish Ah. doi:10.1097/htr.0000000000000765

142. Ponsford JL, Spitz G. Stability of employment over the first 3 years following traumatic brain injury. *J Head Trauma Rehabil*. 2015;30(3):E1-E11. doi:10.1097/HTR.0000000000000033

143. Grauwmeijer E, Heijenbrok-Kal MH, Haitsma IK, Ribbers GM. A prospective study on employment outcome 3 years after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2012;93(6):993-999. doi:10.1016/j.apmr.2012.01.018

144. Cnossen MC, Scholten AC, Lingsma HF, et al. Predictors of major depression and posttraumatic stress disorder following traumatic brain injury: A systematic review and meta-analysis. *J Neuropsychiatry Clin Neurosci*. 2017;29(3):206-224. doi:10.1176/appi.neuropsych.16090165

145. Sjöberg L, Karlsson B, Atti AR, Skoog I, Fratiglioni L, Wang HX. Prevalence of depression: Comparisons of different depression definitions in population-based samples of older adults. *J Affect Disord*. 2017;221(April):123-131. doi:10.1016/j.jad.2017.06.011

146. Nielsen MG, Ørnbøl E, Bech P, Vestergaard M, Christensen KS. The criterion validity of the web-based major depression inventory when used on clinical suspicion of depression in primary care. *Clin Epidemiol*. 2017;9:355-365. doi:10.2147/CLEP.S132913

APPENDICES

Appendix A. List of ICD-10 codes (DRUE)

Diagnostic groups and ICD-10 codes for DRUE

Diagnosis	ICD-10 diagnostic codes
Traumatic brain injury	S020, S021, S027-S029, S061-S071, S097, T020, T040, T060, T903, T905
Stroke including subarachnoid haemorrhages	I60, I61, I63, I64, I67 (except I674), I68, I690-I694, I698
Encephalopathy	B220, E159, E512, G410, G929, G931, G938, G978, I460, O292, O743, O754, O892, T58, T719, T751,
Central nervous system infection	A321, A390, A398, B003, B004, B451, B582, G00, G01, G040, G042, G048, G05, G060, G07-G09
Primary brain tumour	C70-C71, D32, D330, D332, D337, D339
Other comparable diseases	G372, I674, I720

Appendix B. Paper I

Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review

Ryttersgaard TO[a,d], Johnsen SP[b], Riis JØ[c], Mogensen PH[a], Bjarkam CR[c,d].

Scandinavian Journal of Psychology, 2020, 61(2), p. 297-306.

Affiliations:

a) Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
b) Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark
c) Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark
d) Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Scandinavian Journal of Psychology, 2020, 61, 297–306 DOI: 10.1111/sjop.12587

Personality and Social Psychology

Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review

TRINE O. RYTTERSGAARD,[1] SØREN P. JOHNSEN,[2] JENS Ø. RIIS,[3] POUL H. MOGENSEN[4] and CARSTEN R. BJARKAM[5]

[1]*Department of Neurology, Institute of Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark*
[2]*Danish Center for Clinical Health Services Research, Institute of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark*
[3]*Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark*
[4]*Department of Neurology, Aalborg University Hospital, Aalborg, Denmark*
[5]*Department of Neurosurgery, Institute of Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark*

Ryttersgaard, T. O., Johnsen, S. P., Riis, J. Ø., Mogensen, P. H. & Bjarkam, C. R. (2020) Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review. *Scandinavian Journal of Psychology, 61,* 297–306.

To review the prevalence of depression among adolescents and young adults after moderate to severe TBI. A systematic literature search was conducted on literature published up to December 2018 in PubMed, EMBASE, Cochrane and PsychInfo. A systematic review of the identified literature was based on PRISMA guidelines. Risk of Bias was evaluated based on the aspects of Risk of Bias assessment described by the Agency of Health Research and Quality. Seven studies were deemed eligible and information on the prevalence of depression among adolescents and young adults (age 13–35) after moderate to severe TBI was extracted. Depression was assessed at 12 months (n = 2), >12 months (n = 2) or at varying times (n = 3) after TBI. The identified studies reported a prevalence proportion of depression from 1.6% to 60%. The Risk of Bias assessment showed a range of study quality with the selection of subjects and analysis of attrition being problematic. Although literature is sparse and of varying quality, depression was found to be common among adolescents and young adults with moderate to severe TBI which implies a need to focus on depression in the rehabilitation process and calls for further research.

Key words: Adolescent, depression, prevalence, systematic review, traumatic brain injury, young adult.

Trine Okkerstrøm Ryttersgaard, Department of Neurology, Aalborg University Hospital, Ladegårdsgade 5, 7th, 9000 Aalborg, Denmark; Tel: +45 51821269; fax: +45 97662212; e-mail: try@rn.dk

INTRODUCTION

Adolescence and young adulthood are life periods with many transitions that are characterized by increasing demands for independency (Meeus, 2016). The challenges of these life periods are unique to this age group as children live in a parent-protected environment while older adults have established themselves in relation to work and family. This means that teenagers and young adults with TBI struggle with expectations from both society and relatives on becoming independent while they are going through the rehabilitation process. This struggle might result in increased vulnerability for the development of depressive disorder that prevent proper rehabilitation as well as impairing psychosocial functioning (Hibbard, Ashman, Spielman, Chun, Charatz & Melvin, 2004) and quality of life (Di Battista, Godfrey, Soo, Catroppa & Anderson, 2014; Juengst, Kumar & Wagner, 2017). It is therefore vital to recognize the prevalence proportion of depression among adolescents and young adults after they have suffered a moderate to severe TBI.

Although most patients with TBI are adolescents and young adults, studies on depression after TBI focus primarily on adults (Guillamondegui, Montgomery, Phibbs et al., 2011; Osborn, Mathias & Fairweather-Schmidt, 2014; van Reekum, Cohen & Wong, 2000; Sasse, Gibbons, Wilson et al., 2014). To our knowledge, no reviews or meta-analyses on depression among adolescents and young adults age 13–35 years with moderate to severe TBI can be found in the literature. When looking at the studies of the adult population of patients with TBI, depression varies substantially from approximately 5.3% (Koponen, Taiminen, Hiekkanen & Tenovuo, 2011) to 76.6% (Varney, Martzke & Roberts, 1987); moreover, pooled prevalence estimates of depression among adults with TBI vary from 17% in the first year after TBI to 43% in the long-term (Scholten, Haagsma, Cnossen, Olff, van Beeck & Polinder, 2016). It is interesting to note that Guillamondegui et al. (2011) found a weighted average for prevalence of depression on 31% for adults regardless of time-since-injury and depression measures. Estimates of depression prevalence have been reported to be between 5.3% and 36% (Laliberté Durish, Pereverseff & Yeates, 2017) when looking at children and adolescents aged 0–18 years. The lower variance in the prevalence proportion of depression among children and adolescents aged 0–18 years with TBI compared to adults with TBI could reflect a general lower risk of developing a depression after TBI or be the result of fewer studies conducted among children and adolescents. It might, however, also reflect that this younger age group live in parent protected environments.

The displayed variation discussed above could reflect the use of different diagnostic tools, inconsistencies in depression diagnosis or pooling of brain injury severities (i.e., the population consisted of mild, moderate and severe TBI) (Guillamondegui et al., 2011; Osborn et al., 2014; Scholten et al., 2016). Thus, studies on depression after mild TBI report a prevalence of depression around 10–15% (Meares, Shores, Taylor et al., 2011; Ponsford, Cameron, Fitzgerald, Grant & Mikocka-Walus, 2011; Rao, Bertrand,

Rosenberg et al., 2010). The displayed variation might also depend on the timing of the occurrence of depression, for example, some studies investigate post-TBI depression, which is defined as depression that has developed after TBI, while other studies investigate depression in the TBI population regardless of whether the depression was present before the TBI. This distinction is particularly important because inclusion of participants with pre-TBI depression may elevate the prevalence proportion of depression after TBI as having depression before the TBI might increase the risk for depression after injury (Bombardier, Fann, Temkin, Esselman, Barber & Dikmen, 2010). The displayed variation might equally well be dependent on the definition of depression. Thus, to ensure that all relevant studies were included, this review used a broad definition of depression that included both depression diagnosed by the *Diagnostic and statistical manual of mental disorders* – 4ed (DSM-IV) (American Psychiatric Association, 1995) and the International statistical classification of diseases and related health problems – 10th edition (ICD-10) (World Health Organization, 2016), as well as depression described by clinically significant depressive symptoms.

In 2012, the Danish Ministry of Health and Elderly allocated money to investigate the need of rehabilitation among 15–30 year old survivors of an acquired brain injury. This, along with the fact that adolescence and young adulthood are life periods with many transitions and increasing demands for independency, are the reasons why this specific age group was chosen for the review aiming to identify existing knowledge about the prevalence of depression after moderate to severe TBI among adolescents and young adults age 15–30 years.

METHODS

The review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and meta-analyses) (Moher, Liberati, Tetzlaff & Altman, 2009) guidelines, and a protocol was developed before the search was conducted (cf. Data S1).

Search strategy

Relevant studies were identified through systematic literature searches in PubMed, EMBASE, PsychINFO and Cochrane. To ensure that all relevant studies were identified, the search was conducted without any specific time limits. The searches were imported in RefWorks and duplicate material was removed.

Search strategies were developed in consultation with a librarian and search specialist (please see Acknowledgement), and the search included a combination of subheadings and text words which are shown in the Appendix A and B.

PsychINFO subheadings differed from those in PubMed, EMBASE and Cochrane and were included because prevalence of depression was the focus of this review. Reference lists for included articles and relevant reviews were analyzed to identify additional relevant citations.

Study selection

Inclusion criteria. A study was evaluated as eligible if it fulfilled the inclusion criteria listed below concerning study design, participants and outcome measure.

Study design. Retrospective and prospective cohort, case-control and cross-sectional studies.

Participants. Our target group was those who were 15–30 years old at time of injury and had moderate to severe TBI. As none of the identified studies had a study cohort in the exact age range we were looking for (15–30 years), we decided to include studies with an age range of 13–35 years; thus, studies with either a wider or more narrow age-range were included if a prevalence of depression could be extracted for the included age group.

Within our definition of moderate to severe TBI, all patients with (1) an acute Glasgow Coma Scale (GCS) below 13 (Andriessen, Jacobs & Vos, 2010; Teasdale & Jennett, 1974), and those who had (2) an acute GCS above 12 and an abnormal computed tomography (CT) scan of cerebrum were included. The literature refers to the latter as complicated mild TBI and is included as studies have shown that sequelae after GCS > 12 and an abnormal CT-scan of the cerebrum more closely resembles the sequelae from moderate TBI rather than mild TBI (Kashluba, Hanks, Casey & Millis, 2008). A study was included if it was stated that the participants had moderate to severe TBI even if the definition of injury severity was either not reported or deviated from the above mentioned definition (cf. Risk of Bias assessment). This ensured that all relevant studies were included.

Outcome measure. We looked for a prevalence proportion of depression that could be extracted for the included participants regardless of assessment instrument/method.

According to DSM-IV and ICD-10, depression is defined as a major depressive episode (DSM-IV), minor depressive episode (DSM-IV) or depressive episode (ICD-10) (American Psychiatric Association, 1995; World Health Organization, 2016). It is general practice that depression is diagnosed through a diagnostic interview. Many international studies use a self-report questionnaire to identify the degree of depressive symptoms patients experience. Most self-report questionnaires use a cut-off score to identify cases of depression which are described as clinically significant depressive symptoms in the literature. Although participants with clinically significant depressive symptoms may not fulfil the diagnostic criteria for depression, significant knowledge would have been lost if studies that use this method were excluded.

Exclusion criteria. Reviews, case reports, editorials, conference abstracts and intervention studies were excluded. Intervention studies were excluded due to a high risk of selection bias. Articles written in languages other than English were also excluded.

Multiple publications. The included articles were evaluated to see if the same study population was used in more than one study. This was done to avoid counting prevalence rates multiple times. If it was found that the same population was used, the primary publication was included.

Data extraction

The first author (TOR) screened all titles and abstracts. Irrelevant citations were excluded. After the initial screening, the remaining citations were evaluated based on title, abstract and full-text, and citations were included according to the inclusion criteria. All citations evaluated as eligible and studies deemed by the first author to have uncertain inclusion criteria were discussed with the fifth author (CRB).

A data extraction form was developed to ensure that all relevant data were extracted. Data on the following variables were sought in the included articles: study design, country, study location, definition of TBI severity, size of the study population, distribution of gender, age (mean, SD and range), time-since-injury (mean, SD and range), inclusion and exclusion criteria for the study, assessment tool for evaluating depression or depressive symptoms and prevalence proportion of depression/clinically significant depressive symptoms. The first author made the data extraction which was then confirmed by the second author (SPJ). No authors of the identified studies were contacted to evaluate whether the results presented in the articles were correct or whether additional information was available.

Table 1. *Risk of Bias Assessment -description of the assessment criteria*

	Low risk	Unclear risk	High risk
Setting (selection bias)	Multi-center study	Unclear whether it is a single-center or multi-center study	Single-center study
Inclusion criteria (selection bias)	Inclusion and exclusion criteria are well-described	Either inclusion or exclusion criteria is not described	Inclusion and exclusion criteria are not described
Recruitment process (selection bias)	The recruitment process is well-described	The recruitment process is described but unclear	The recruitment process is not described or there has been a selection of contacted subjects
Completeness (attrition bias)	Attrition is reported and it is analyzed whether the included subjects differ from non-participants	There is uncertainty about the reported attrition and the analysis of participants and non-participants	Attrition is not reported and/or not analyzed
Definition of TBI severity (detection bias)	The definition of TBI severity is well-described	TBI severity is not defined, but data on GCS, PTA, coma length orCT-/MR-scan are available in the text	The definition of TBI severity is not described
Method to evaluate depression/ depressive symptoms (detection bias)	Structured interview with description of diagnostic method	Structured interview without description of diagnostic method	Self-report questionnaire
Report of outcome (reporting bias)	The relevant results are reported	The relevant results are reported, but descriptive data or attrition analysis is missing	The relevant results are not reported

Risk of Bias assessment

No specific Risk of Bias (RoB) assessment tool was identified as suitable as the included studies primarily consisted of cross-sectional observational studies. Instead, criteria for the RoB assessment were developed based on the aspects described by Agency of Health Research and Quality (Viswanathan, Ansari, Berkman et al., 2014) which is based on Cochrane Handbook of Systematic Reviews (Higgins & Green, 2011).

RoB was evaluated according to setting (selection bias), inclusion criteria (selection bias), recruitment process (selection bias), completeness (attrition bias), definition of TBI severity (detection bias), method to evaluate depression (detection bias) and report of outcome (reporting bias) and evaluated as "Low risk," "Unclear risk" and "High risk." A description of the evaluation criteria is presented in Table 1. The RoB assessment was conducted by the first author and evaluated by the co-authors.

RESULTS

Literature search

The systematic literature search was conducted on 16 January 2018. The search identified 1,208 potentially relevant, unique titles and was updated 14 December 2018. This search led to identification of 107 new potentially relevant, unique titles. Twenty additional articles were identified through references in the included articles and relevant reviews. Figure 1 shows the PRISMA-flowchart (Moher et al., 2009).

A total of 1,067 articles were excluded after title and abstract screening. Of the remaining 268 articles, 261 were excluded after full text reading. The main reasons for exclusion were: (1) results for patients with moderate to severe TBI could not be identified as they were pooled with patients with mild TBI; (2) results for adolescents and younger adults could not be identified because the younger participants were pooled with participants who were older; and (3) prevalence of depression was not reported. The remaining seven studies identified are the basis of this review.

Study characteristics

Table 2 shows the characteristics of the included studies. Three studies reported a prevalence of depression among adolescents and young adults with moderate to severe TBI (Garske & Thomas, 1992; Tyerman & Humphrey, 1984; Willmott, Spitz & Ponsford, 2015). Two studies had a population study group with a wider age range than our inclusion criteria. Even so, prevalence of depression for participants age 19–30 and age 18–29, respectively, could be extracted (Bombardier et al., 2010; van Reekum, Bolago, Finlayson, Garner & Links, 1996). Two studies reported a prevalence of depression on a more narrow age range – age 14–17 and age 14–18 respectively (O'Connor, Zatzick, Wang et al., 2012; Poggi, Liscio, Adduci et al., 2003).

The studies were conducted in five different countries: the United States (US) (n = 3) (Bombardier et al., 2010; Garske & Thomas, 1992; O'Connor et al., 2012), Canada (n = 1) (van Reekum et al., 1996), the United Kingdom (UK) (n = 1) (Tyerman & Humphrey, 1984), Italy (n = 1) (Poggi et al., 2003) and Australia (n = 1) (Willmott et al., 2015). Five studies were cross-sectional studies with only one assessment of depression (Garske & Thomas, 1992; Poggi et al., 2003; van Reekum et al., 1996; Tyerman & Humphrey, 1984; Willmott et al., 2015). Two studies were prospective studies with consecutive examinations in the same population (Bombardier et al., 2010; O'Connor et al., 2012). Participants were recruited from an acute trauma center (n = 1) (Bombardier et al., 2010), different hospitals (n = 1) (O'Connor et al., 2012) and a rehabilitation center/program (n = 5) (Garske & Thomas, 1992; Poggi et al., 2003; van Reekum et al., 1996; Tyerman & Humphrey, 1984; Willmott et al., 2015).

The sample size varied from 10 to 175. Demographics were available in six of the seven studies, but O'Connor et al. (2012) did not report data on age for the defined trauma groups. Bombardier et al. (2010) reported demographic information for

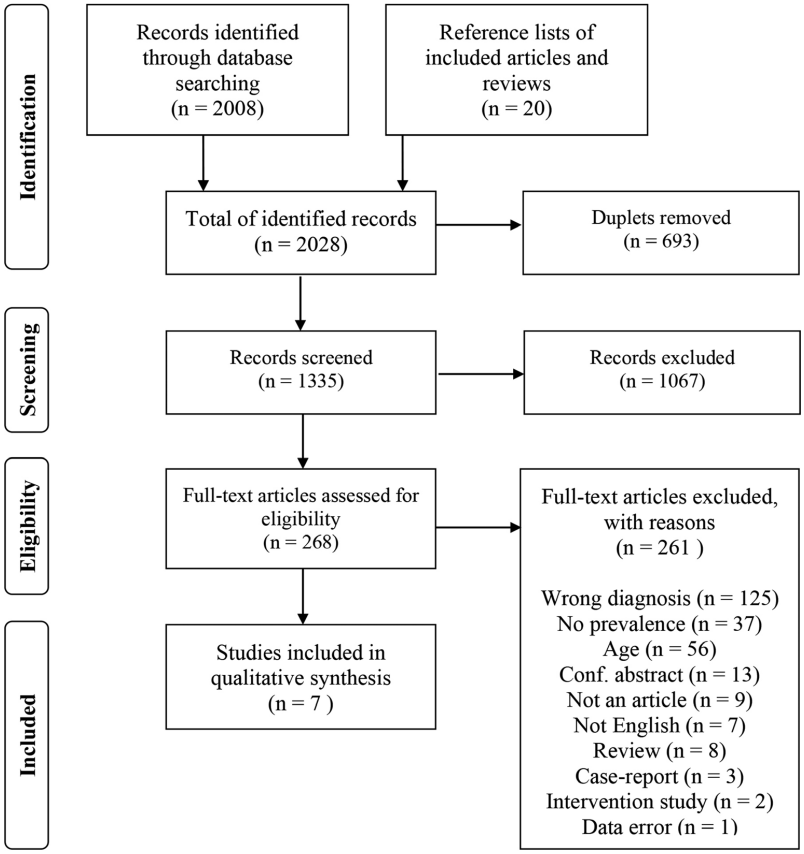

Fig. 1. Prisma flow diagram – study selection.

the whole study population and not according to the defined age groups. In the five studies reporting on age, the mean age varied from 15.8 to 23.4 years, and the ages ranged from 13 to 35 (Garske & Thomas, 1992; Poggi et al., 2003; van Reekum et al., 1996; Tyerman & Humphrey, 1984; Willmott et al., 2015). The majority of the participants were male and were 60–93% of the populations studied (Garske & Thomas, 1992; O'Connor et al., 2012; Poggi et al., 2003; Tyerman & Humphrey, 1984; van Reekum et al., 1996; Willmott et al., 2015). TBI severity was defined by either GCS and/or abnormal CT-scan of cerebrum (Bombardier et al., 2010; O'Connor et al., 2012; Poggi et al., 2003) or length of post traumatic amnesia (PTA) (Tyerman & Humphrey, 1984; Willmott et al., 2015). In two studies, the definition of TBI severity was not reported. In accordance with time-since-injury, two studies reported 12 months post-injury prevalence (Poggi et al., 2003; Willmott et al., 2015) while one study reported prevalences of 3, 12 and 24 months post-injury (O'Connor et al., 2012). Another study used five consecutive measurements to calculate how many participants developed MDD during the first 12 months after injury (Bombardier et al., 2010). One study included participants who were 2–15 months post-injury (Tyerman & Humphrey, 1984), and two studies were long-term follow-up (>12 months) (Garske & Thomas, 1992; van Reekum et al., 1996).

The studies used different assessments methods to screen for depression. Specifically, one study used a semi-structured interview made by an experienced psychiatric nurse (van Reekum et al., 1996), and another study used a structured interview based in PHQ-9 (Bombardier et al., 2010).The remaining studies used five different self-report questionnaires in which only the PHQ-9 and the Test of Anxiety and Depression in childhood and adolescence (TAD) were based on the diagnostic criteria for depression (Garske & Thomas, 1992; O'Connor et al., 2012; Poggi et al., 2003; Tyerman & Humphrey, 1984; Willmott et al., 2015).

Risk of Bias (RoB)

Figure 2 shows the RoB assessment. The RoB assessment showed that the identified studies had from one high risk assessment (Willmott et al., 2015) up to as many as five high risk assessments (Poggi et al., 2003). The main problem with the seven studies is knowing to what extend the results can be generalized to the whole population of adolescents and young adults with moderate to severe TBI. Willmott et al. (2015) was evaluated as having the

Table 2. *Characteristics of the seven-included studies*

Author, year, country, design	Study population	Inclusion (I)/exclusion (Ex)	Sample	Assessment
Bombardier et al., 2010, US, Prospective	Compl. mild to severe TBI, Level 1 trauma center (n = 175)	I: >18 y Ex: Uncompl. mTBI (GCS: 13–15 & no radio 1. abnorm)	18–29 y Demographics not available for the age group 18–29 y	Structured interview based on PHQ-9
Garske & Thomas, 1992, US, Cross-sectional	Severe TBI, Acute rehab. center, (n = 47)		22.9 y (5.5), 16–35; male 68%	BDI
Poggi et al., 2003, Italy, Cross-sectional	Moderate to severe TBI Rehab, center (n = 64)	I: 0–18 y, admission at max. 1 y from trauma E: positive history of previous brain injury, behavioural and psychological disorders, previous brain lesions, preexisting acute and chronic serious illness, vegetative state	15.8 y (1.48), 14–18; Male 77%	The first scale of the TAD
O'Connor et al., 2012 US, Prospective	Compl. mild (Mild II) to severe TBI, Nine hospitals (n = 64)	I: 14–17 y, discharged alive between March 1, 2007 and September 30, 2008	Age is not available for the two incl. groups male 72%	PHQ-9
Tyerman & Humphrey, 1984, UK, Cross-sectional	Severe TBI Rehab, center, (n = 22)	Ex: severe communication disorder	22, 17–34; male 93%	The Leeds scale of depression
van Reekum et al., 1996 Canada, Cross-sectional	Mild to severe TBI (only pts with moderate to severe TBI incL in current review) Rehab. program, (n = 10)	I: TBI secondary to MVA >2 y prior to study; Age <50 y; Suff. language, motor & perceptual skills to permit test; Lack of pre-TBI psychiatric history; Living in the community	23.4, 19–30; male 60%	Semi- structured interview SADS-L
Willmott et al., 2015, Australia, Cross-sectional	Compl. mild to severe TBI, Rehab, center, (n = 145)	I: students prior to injury	18.6 y (3.29), 13–34; male 64.1%	The Struct. outcome question

Notes: TAD, test of anxiety and depression in childhood and adolescence; PHQ-9, patient 60health questionnaire-9; BDI, beck depression inventory; SADS-L, schedule of affective disorder and schizophrenia-L; y, year.
[a]Age at assessment.

lowest RoB; however, the study focuses solely on individuals who were students prior to the injury and may therefore not be generalized to similarly aged TBI patients with different socioeconomic backgrounds. O'Connor et al. (2012) and Tyerman and Humphrey (1984) are the only multi-center studies among the included studies. In both studies, the recruitment process is unclear and attrition analyses were not reported. Thus, the results of the seven identified studies must be evaluated as a prevalence of depression for their specific sample and not the general population of adolescents and young adults with moderate to severe TBI (Bombardier et al., 2010; Garske & Thomas, 1992; O'Connor et al., 2012; Poggi et al., 2003; Tyerman & Humphrey, 1984; van Reekum et al., 1996; Willmott et al., 2015).

Prevalence proportion of depression

Table 3 reports the prevalence of depression and calculated 95% CI according to study and time-since-injury. The seven studies reported a prevalence of depression from 1.6% to 60% with assessment ranging from 3-month post-injury up to nine years after injury. At twelve months post-injury, the prevalence of depression varied from 13% to 39.3% (Poggi et al., 2003; Willmott et al., 2015). Long-term prevalence varied from 55.3% to 60% (Garske & Thomas, 1992; van Reekum et al., 1996). Tyerman and Humphrey (1984) found a prevalence of 60% two-fifteen months post-injury; and Bombardier et al. (2010) reported that during the first year after TBI, 52.6% of patients met criteria for MDD. O'Connor et al. (2012) found a stable and very low prevalence proportion of 1.6% among 14–17-year old adolescents at 3, 12 and 24 months post-injury.

A pooled prevalence proportion of depression has not been made due to the limitations of the individual studies on the generalizability of the results.

DISCUSSION

As no more than seven relevant studies were identified, this systematic literature review revealed limited existing knowledge on depression after moderate to severe TBI among adolescents and young adults. The primary reasons for exclusion of studies were due to pooling of severity and age as most studies included patients with mild, moderate and severe TBI and older life periods than our specified age group of 13–35 years. The included studies showed a high variation as O'Connor et al. (2012) found a very low prevalence of depression among patients (1.6%) while Tyerman and Humphrey (1984) and van Reekum et al. (1996) found prevalence proportions of 60%. A similar variation-span is seen in reviews on adults with TBI

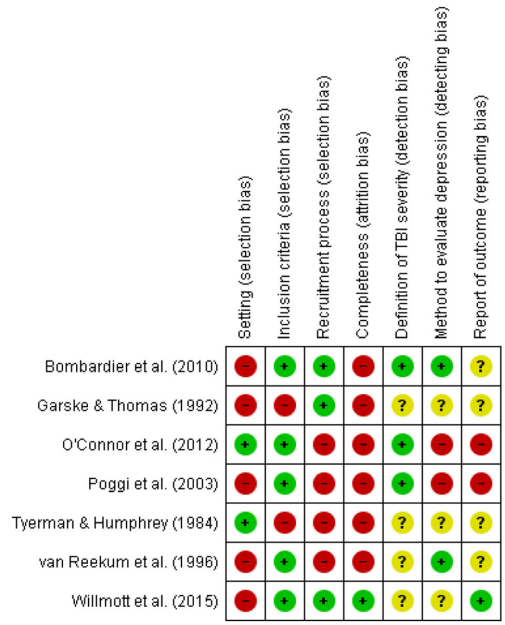

Fig. 2. Overview risk of bias assessment. "+" = "Low risk," "?" = "Unclear risk," "-" = "High risk." [Colour figure can be viewed at wileyonlinelibrary.com]

(Guillamondegui et al., 2011; Osborn, Mathias, Fairweather-Schmidt & Anstey, 2017; Scholten et al., 2016).

A pooled prevalence estimate was not calculated because the RoB assessment showed several limitations in the identified studies and their results may not, consequently, describe the general population of adolescents and young adults with a moderate to severe TBI. The primary limitations of the included studies were about selection of the study population and data completeness. An obscure recruitment process that is caused by selection of the participants or missing inclusion criteria can result in a questionable low or high prevalence of depression. Likewise, a missing attrition analysis can make it impossible to evaluate whether a difference between the non-attendees and the study population could have influenced the results. Accordingly, the generalizability of the results can also be affected by small study populations as this can result in questionable prevalence proportions of depression (Tyerman & Humphrey, 1984; van Reekum et al., 1996).

The limitations of the included studies can be one of the reasons for the high variation in the prevalence of depression as the studies reporting low and high prevalence proportions had the highest risk of biases. The variation could furthermore be the result of the application of different methods to evaluate the prevalence of depression. Hence, five of the studies used a self-report questionnaire which rated the amount of depressive symptoms instead of using the diagnostic criteria for depression (Garske & Thomas, 1992; O'Connor et al., 2012; Poggi et al., 2003; Tyerman & Humphrey, 1984; Willmott et al., 2015). This tendency was also observed in studies of the adult population (Osborn et al., 2014). The use of a cut-off score may elevate the prevalence proportion of depression because a patient can be evaluated as having depression without fulfilling the diagnostic criteria. In the same way, five consecutive assessments in the first year post-injury may also elevate the prevalence proportion of depression (Bombardier et al., 2010). Finally, the variation could illustrate a difference in the prevalence of depression among adolescents and young adults with the included studies indicating that young adults have higher prevalence of depression (Bombardier et al., 2010; Garske & Thomas, 1992; Tyerman & Humphrey, 1984; van Reekum et al., 1996; Willmott et al., 2015) than adolescents do (O'Connor et al., 2012; Poggi et al., 2003). Such a difference can be related to the demands of independency which increase from adolescence to young adulthood as part of psychosocial development (Erikson, 1950). The transition from childhood to adulthood and demands on independency is contextually and culturally dependent (Pao, 2017), and the prevalence of depression may increase at the same pace as the transition from a parent protected life to adult independency.

Overall, this review finds that there is a tendency among young survivors of a moderate to severe TBI of having increased risk of depression compared to the general population of adolescents and young adults. This is supported by the fact that six of the seven studies explored in this review found a higher prevalence proportion of depression than reported in studies of the general population. The EU-WMH project, which is based on data from 10 European countries, found a prevalence of depression of 5.2% among the 18–34-year old participants (Bruffaerts, Vilagut, Demyttebaere et al., 2009) which corresponds to the Global Health Estimates of depression of 3–6.5% within the 15–29-year old general population (World Health Organization, 2017).

Table 3. *Prevalence (%) of depression and time to follow-up. m = month; y = year*

		Prevalence (%) according to time of follow-up					
Study	Severity	<1 year	1 year	>1 year	Varies	95% CI	Follow-up mean (SD), *range*
Bombardier et al. (2010)	Compl. mild to severe				52.6[a]	44.9–60.2	1 m, 6 m, 8 m, 10 m, 1 y
Garske & Thomas (1992)	Severe			55.3		40.1–69.8	49.9 m (22.2), *16–97 m*
Poggi et al. (2003)	Moderate to severe		13			5.6–23.2	1 y
O'Connor et al. (2012)	Compl. mild to severe	1.6	1.6	1.6		0.0–8.4	3 m, 1 y, 2 y
Tyerman & Humphrey (1984)	Severe				60	36.4–79.3	7 m, *2–15 m*
van Reekum et al. (1996)	Moderate to severe			60		26.2–87.8	4.9 y, *2–9 y*
Willmott et al. (2015)	Compl. mild to severe		39.3			31.3–47.8	1 y

Note: Met MDD criteria in minimum one of 5 assessments during the first year after injury.

An increased risk of depression after a moderate to severe TBI in this group when compared to the general population may be related to a delay in the transition from adolescence into young adulthood as the sequelae from the TBI can limit the opportunity to gain independency, education and attachment to the labor market (Tibæk, Kammersgaard, Johnsen, Dehlendorff & Forchhammer, 2019). Moreover, an increased risk of depression could also be the result of peer victimization (Hung, Cassedy, Schultz et al., 2017) which appears to be related to psychosocial maladjustment and depression in adolescents without TBI (Hawker & Boulton, 2000). Taken together, it appears to be vital to focus on the significance of depression among adolescents and young adults with moderate to severe TBI as depression may complicate or delay the rehabilitation process (Bombardier et al., 2010; Hudak, Hynan, Harper & Diaz-Arrastia, 2012).

Strengths and limitations

The review was based on a thorough and systematic literature search. A limitation of the study is that one author had the primary responsibility for the selection process. Additionally, only the included studies and studies with doubt about inclusion were screened by a second author. This could have increased the risk of subjective assessment and affected the result of the study selection process.

Our choice to only include studies with adolescents and young adults approximately age 15–30 had both strengths and limitations. An opportunity to obtain knowledge about the existing literature on prevalence of depression in the defined age group was provided which has a special relevance as the proportion of TBI is relative high in this age group. The primary limitation of the limited age range is the fact that we identified very few studies and based on the Risk of Bias assessment, we did not calculate a pooled prevalence proportion.

Complicated mild TBI was included in the definition of moderate to severe TBI, as studies have shown that the sequelae of complicated mild TBI resembles the sequelae from moderate TBI rather than mild TBI (cf. Methods). This could both be a strength and a limitation, as it increased the number of identified studies but could have had an impact on the overall findings. The studies, which included patients with complicated mild TBI are the most recent studies and may illustrate a future definition of moderate to severe TBI. Finally, the fact that pre-TBI depression was not an exclusion criterion could be a study limitation, as inclusion of patients with pre-TBI depression may elevate the prevalence proportion of depression (see, for example the Introduction).

Implications for future research and clinical practice

Our work revealed a need of further studies on depression among adolescent and young adult survivors of moderate to severe TBI. Prospective multi-center studies on depression after moderate to severe TBI in well-defined cohorts is warranted to ensure knowledge about which patients are at risk of developing depression, the time-perspective for the development of a depression and to ensure that treatment of depressive symptoms is part of the rehabilitation programs. Although it is more time-consuming than using self-report questionnaires, a clinical diagnostic interview is the gold standard for diagnosing depression and is recommended for future studies. Further studies are also needed to evaluate whether adolescents and young adults differentiate from other age groups when it comes to depression after moderate to severe TBI.

Although, the review revealed limited data on depression among adolescents and young adults with moderate to severe TBI the results of the review demonstrate a need to allocate attention to and identify symptoms of depression among young survivors of moderate to severe TBI. If such symptoms are found, pharmacological and/or non-pharmacological interventions should be initiated to support the rehabilitation process.

CONCLUSIONS

Seven primary studies were identified from which a prevalence of depression among adolescents and young adult with moderate to severe TBI could be extracted. The individual prevalence proportions varied from 1.6% to 60%, however, the Risk of Bias assessment showed varying quality and the generalizability of the studies was questionable; consequently, a pooled prevalence estimate was not calculated. Overall, there is need for further studies to determine to what degree young survivors of moderate to severe TBI struggle with depression which can compromise the rehabilitation process.

The authors acknowledge the help from Jette Frost, librarian at Aalborg University Hospital: Ms. Frost helped with the development of the search strategies and the execution of the systematic literature search. The authors have no conflicts of interest to delare.

REFERENCES

American Psychiatric Association (1995). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed). Washington DC: American Psychiatric Association.

Andriessen, T. M. J. C., Jacobs, B. & Vos, P. E. (2010). Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *Journal of Cellular and Molecular Medicine*, *14*, 2381–2392.

Bombardier, C. H., Fann, J. R., Temkin, N. R., Esselman, P. C., Barber, J. & Dikmen, S. S. (2010). Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA*, *303*, 1938–1945.

Bruffaerts, R., Vilagut, G., Demyttebaere, K., Alonso, J., Barbaglia, G., Boyd, A. *et al*. (2009). The burden of mental disorders in the European Union – The EU contribution to the World Mental Health Surveys Initiative. Retrieved 30 August 2019 from http://www.eu-wmh.org/

Di Battista, A., Godfrey, C., Soo, C., Catroppa, C. & Anderson, V. (2014). Depression and health related quality of life in adolescent survivors of a traumatic brain injury: A pilot study. *PLoS ONE*, *9*, e101842.

Erikson, E. H. (1950). *Childhood and society*. New York: Norton.

Garske, G. G. & Thomas, K. R. (1992). Self-reported self-esteem and depression: Indexes of psychological adjustment following severe traumatic brain injury. *Rehabilitation Counseling Bulletin*, *36*, 44–52.

Guillamondegui, O., Montgomery, S., Phibbs, F., McPheeters, M., Alexander, P., Jerome, R. *et al*. (2011). *Traumatic brain injury and depression. Comparative effectiveness review number 25*. Rockville, MD: Agency for Healthcare Research and Quality.

Hawker, D. S. J. & Boulton, M. J. (2000). Twenty years' research on peer victimization and psychosocial maladjustment: A meta-analytic review of cross-sectional studies. *Journal of Child Psychology and Psychiatry*, *41*, 441–455.

Hibbard, M. R., Ashman, T. A., Spielman, L., Chun, D., Charatz, H. J. & Melvin, S. (2004). Relationship between depression and psychosocial functioning after traumatic brain injury. *Annals of Physical and Rehabilitation Medicine*, *85*, S43–S53.

Higgins, J. & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions version 5.1.0*. The Cochrane Collaboration. Available 8 May 2019 from http://handbook.cochrane.org.

Hudak, A. M., Hynan, L. S., Harper, C. R. & Diaz-Arrastia, R. (2012). Association of depressive symptoms with functional outcome after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *27*, 87–98.

Hung, A. H., Cassedy, A., Schultz, H. M., Yeates, K. O., Taylor, H. G., Stancin, T. *et al*. (2017). Predictors of long-term victimization after early pediatric traumatic brain injury. *Journal of Developmental and Behavioral Pediatrics*, *38*, 49–57.

Juengst, S. B., Kumar, R. G. & Wagner, A. K. (2017). A narrative literature review of depression following traumatic brain injury: prevalence, impact, and management challanges. *Psychological Research and Behavior Management*, *10*, 175–186.

Kashluba, S., Hanks, R. A., Casey, J. E. & Millis, S. R. (2008). Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *89*, 904–911.

Koponen, S., Taiminen, T., Hiekkanen, H. & Tenovuo, O. (2011). Axis I and II psychiatric disorders in patients with traumatic brain injury: A 12-month follow-up study. *Brain Injury*, *25*, 1029–1034.

Laliberté Durish, C., Pereverseff, R. S. & Yeates, K. O. (2017). Depression and depressive symptoms in pediatric traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *33*, E18–E30.

Meares, S., Shores, E. A., Taylor, A. J., Batchelor, J., Bryant, R. A., Baguley, I. J. *et al*. (2011). The prospective course of postconcussion syndrome: The role of mild traumatic brain injury. *Neuropsychology*, *25*, 454–465.

Meeus, W. (2016). Adolescent psychosocial development: A review of longitudinal models and research. *Developmental Psychology*, *52*, 1969–1993.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*, *62*, 1006–1012.

O'Connor, S. S., Zatzick, D. F., Wang, J., Temkin, N., Koepsell, T. D., Jaffe, K. M. *et al*. (2012). Association between posttraumatic stress, depression, and functional impairments in adolescents 24 months after traumatic brain injury. *Journal of Traumatic Stress*, *25*, 264–271.

Osborn, A. J., Mathias, J. L. & Fairweather-Schmidt, A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews*, *47*, 1–15.

Osborn, A. J., Mathias, J. L., Fairweather-Schmidt, A. K. & Anstey, K. J. (2017). Anxiety and comorbid depression following traumatic brain injury in a community-based sample of young, middle-aged and older adults. *Journal of Affective Disorders*, *213*, 214–221.

Pao, M. (2017). Conceptualization of Success in Young Adulthood. *Child and Adolescent Psychiatric Clinics of North America*, *26*, 191–198.

Poggi, G., Liscio, M., Adduci, A., Galbiati, S., Sommovigo, M., Degrate, A. *et al*. (2003). Neuropsychiatric sequelae in TBI: A comparison across different age groups. *Brain Injury*, *17*, 835–846.

Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M. & Mikocka-Walus, A. (2011). Long-term outcomes after uncomplicated mild traumatic brain injury: A comparison with trauma controls. *Journal of Neurotrauma*, *28*, 937–946.

Rao, V., Bertrand, M., Rosenberg, P., Makley, M., Schretlen, D. J., Brandt, J. & Mielke, M. M. (2010). Predictors of new-onset depression after mild traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*, 100–104.

Sasse, N., Gibbons, H., Wilson, L., Martinez, R., Sehmisch, S., Von Wild, K. & Von Steinbüchel, N. (2014). Coping strategies in individuals after traumatic brain injury: Associations with health-related quality of life. *Disability and Rehabilitation*, *36*, 2152–2160.

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F. & Polinder, S. (2016). Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: A systematic review. *Journal of Neurotrauma*, *33*, 1969–1994.

Teasdale, G. & Jennett, B. (1974). Assessment of coma and impaired consciousness. *The Lancet Neurology*, *304*, 81–84.

Tibæk, M., Kammersgaard, L. P., Johnsen, S. P., Dehlendorff, C. & Forchhammer, H. B. (2019). Long-term return to work after acquired brain injury in young Danish adults: A nation-wide registry-based cohort study. *Frontiers in Neurology*, *9*, 1–9.

Tyerman, A. & Humphrey, M. (1984). Changes in self-concept following severe head injury. *International Journal of Rehabilitation Research*, *7*, 11–23.

van Reekum, R., Bolago, I., Finlayson, M. A. J., Garner, S. & Links, P. S. (1996). Psychiatric disorders after traumatic brain injury. *Brain Injury*, *10*, 319–328.

van Reekum, R., Cohen, T. & Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*, 316–327.

Varney, N. R., Martzke, J. S. & Roberts, R. J. (1987). Major depression in patients with closed head injury. *Neuropsychology*, *1*, 7–9.

Viswanathan, M., Ansari, M., Berkman, N., Chang, S., Hartling, L., McPheeters, L. *et al*. (2014). Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In *Agency for healthcare research and quality methods guide for comparative effectiveness reviews* (pp. 1–33). Rockville: Agency for Healthcare Research and Quality. Available 02 October 2019 from http://www.effectivehealthcare.ahrq.gov

Willmott, C., Spitz, G. & Ponsford, J. L. (2015). Predictors of productivity outcomes for secondary and tertiary students following traumatic brain injury. *Brain Injury*, *29*, 929–936.

World Health Organization. (2016). *ICD-10: International statistical classification of diseases and related health problems*. Geneva: World Health Organization.

World Health Organization (2017). *Depression and other common mental disorders: Global health estimates*. Retrieved 30 August 2019 from https://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/

Received 30 January 2019, accepted 5 September 2019

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Data S1. Systematic review protocol.

APPENDIX A: LITERATURE SEARCH STRATEGIES

PubMed

("Brain Injuries"[Mesh] OR traumatic brain injur*[Text Word] OR brain contus*[Text Word] OR traumatic brain hemorrhag*[Text Word] OR diffuse axonal[Text Word] OR diffuse brain injur*[Text Word]) AND ("Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR depressi*[Text Word]) AND ("Adolescent"[Mesh] OR "Young Adult"[Mesh] OR adolescen*[Text Word] OR young adult*[Text Word] OR youngster*[Text Word])

Embase

(traumatic brain injury/exp OR traumatic brain injur* (ti.ab.kw) OR brain contus* OR traumatic brain hemorrha* OR diffuse axonal OR diffuse brain injur*) AND (depression/exp OR depressi*) AND (adolescent/exp OR young adult/exp OR (adolescen* OR young adult* OR youngster))

Cochrane

(Brain Injuries [MeSH] OR traumatic brain injur* (ti,ab,kw) OR brain contus* (ti,ab,kw) OR traumatic brain hemorrhag* (ti,ab, kw) OR diffuse axonal (ti,ab,kw) OR diffuse brain injur* (ti,ab,

kw)) AND (Depressive Disorder [MeSH] OR Depression [MeSH] OR depressi* (ti,ab,kw)) AND (Adolescent [MeSH] OR Young Adult [MeSH] OR adolescen* (ti,ab,kw) OR young adult* (ti,ab, kw) OR youngster* (ti,ab,kw))

PsychInfo

(((**IndexTermsFilt**: (“Depression (Emotion))” *OR(***IndexTerms Filt**: (“Major Depression”)) *OR (***IndexTermsFilt**: (“Anaclitic Depression”)) *OR (***IndexTermsFilt**: (“Dysthymic Disorder”)) *OR (***IndexTermsFilt**: (“Endogenous Depression”)) *OR (***IndexTerms Filt**: (“Late Life Depression”)) *OR (***IndexTermsFilt**: (“Postpartum Depression”)) *OR (***IndexTermsFilt**: (“Reactive Depression”)) *OR (***IndexTermsFilt**: (“Recurrent Depression”)) *OR (***IndexTermsFilt**: (“Treatment Resistant Depression”)) *OR* (**title**: (depressi*)) *OR* (**abstract**: (depressi*)) *OR* (**Keywords**: (depressi*))) *AND* ((**IndexTermsFilt**: (“Traumatic Brain Injury”)) *OR* (**IndexTerms Filt**: (“Head Injuries”)) *OR* ((**title**: (traumatic brain injur*)) *OR* (**abstract**: (traumatic brain injur*)) *OR* (**Keywords**: (traumatic brain injur*)) *OR* (**Any Field**: (“diffuse brain injur*”)) *OR* (**Any Field**: (“brain contus*”)) *OR* (**Any Field**: (“traumatic brain hemorrhag*”)) *OR* (**Any Field**: (“diffuse axonal”)) *AND* (**AgeGroupFilt**: “Young Adulthood (18-29 yrs)”)) *OR (*(((**Index TermsFilt**: (“Depression (Emotion))” *OR(***IndexTermsFilt**: (“Major Depression”)) *OR (***IndexTermsFilt**: (“Anaclitic Depression”)) *OR (***IndexTermsFilt**: (“Dysthymic Disorder”)) *OR (***IndexTermsFilt**: (“Endogenous Depression”)) *OR (***IndexTerms Filt**: (“Late Life Depression”)) *OR (***IndexTermsFilt**: (“Postpartum Depression”)) *OR (***IndexTermsFilt**: (“Reactive Depression”)) *OR (***IndexTermsFilt**: (“Recurrent Depression”)) *OR (***IndexTermsFilt**: (“Treatment Resistant Depression”)) *OR* (**title**: (depressi*)) *OR* (**abstract**: (depressi*)) *OR* (**Keywords**: (depressi*))) *AND* ((**Index TermsFilt**: (“Traumatic Brain Injury”)) *OR* (**IndexTermsFilt**: (“Head Injuries”)) *OR* ((**title**: (traumatic brain injur*)) *OR* (**abstract**: (traumatic brain injur*)) *OR* (**Keywords**: (traumatic brain injur*)) *OR* (**Any Field**: (“diffuse brain injur*”)) *OR* (**Any Field**: (“brain contus*”)) *OR* (**Any Field**: (“traumatic brain hemorrhag*”)) *OR* (**Any Field**: (“diffuse axonal”)) *AND* ((**title**: (adolescen*)) *OR* (**abstract**: (adolescen*)) *OR* (**Keywords**: (adolescen*)) *OR* (**title**: (“young adult*”)) *OR* (**abstract**: (“young adult*”)) *OR* (**Keywords**: (“young adult*”)) *OR* (**title**: (youngster*)) *OR* (**abstract**: (youngster*)) *OR* (**Keywords**: (youngster*))))

APPENDIX B: KEYWORDS LITERATURE SEARCH FOR THE ORIGINAL SEARCH CONDUCTED 16 JANUARY 2018

#	Search	PubMed	Embase	Cochrane	PsychInfo
1	Brain Injuries [Mesh]/traumatic brain injury [exp]/Traumatic Brain Injury OR Head Injury	60,019	36,887	1,459	19,575
2	traumatic brain injur*	29,512	43,022	2,312	19,048
3	brain contus*	574	3,564	106	52
4	traumatic brain hemorrhag*	212	25	247	35
5	diffuse axonal	1,479	2,334	51	403
6	diffuse brain injur*	367	565	108	114
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	69,582	54,502	3,041	22,360
8	Depressive Disorder [Mesh]/Major Depression [Index Terms]	97,072		9,173	117,279
9	Depression [Mesh/exp/Index Terms]	98,419	416,405	7,550	24,274
10	depressi*	398,839	598,481	51,315	266,564
11	#8 OR #9 OR #10 #9 OR #10	399,487	632,417	51,360	266,815
12	#7 AND #11	2,520	4,220	254	1,803
13	Adolescent [MESH] OR Young Adult [MESH]	2,121,344			*
14	young adult [MESH/exp]		211,969	93,491	
15	Adolescent [MESH/exp]		1,466,172	275	
16	adolescen* OR young adult OR youngster	2,217,562	1,787,177		279,792
17	Adolescen*			119,862	
18	Young adult*			74,453	
19	Youngster*			105	
20	#13 OR #16/#14 OR #15 OR #16/#14 OR #15 OR #16 OR #17 OR #18 OR #19	2,217,562	1,787,177	163,126	279,792*
21	#12 AND #20	692	522	53	607

Note: *Index terms on age are not available in PsychInfo. Age filters are used in the final search

SYSTEMATIC REVIEW PROTOCOL

Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic Review

TABLE OF CONTENTS

Administrative information

1. Title

1.a Identification

This is a protocol for the systematic review:

Prevalence of depression after moderate to severe traumatic brain injury among adolescents andyoung adults.

1.b Update

No previous systematic review has been identified.

2. Registration

The protocol is not registered

3. Authors

3.a Contact

Trine Okkerstrøm Ryttersgaard (corresponding author), MSc, Psychologist, PhD-student, Department of Neurology, Institute of Clinical Medicine, Aalborg University Hospital,Ladegårdsgade 5, 7th, 9000 Aalborg, Denmark, try@rn.dk

Søren Paaske Johnsen, PhD, MD, Professor, Danish Center for Clinical Health Services Research, Institute of Clinical Medicine, Aalborg University and Aalborg University Hospital,Denmark, soeren.johnsen@rn.dk

Jens Østergaard Riis, MSc, Psychologist, Chief of Neuropsychology, Department of Neurosurgery,Aalborg University Hospital, Denmark, jeor@rn.dk

Poul Henning Mogensen, PhD, MD, Head of department, Department of Neurology, AalborgUniversity Hospital, Denmark, poul.mogensen@rn.dk

Carsten Reidies Bjarkam, PhD, MD, Professor, Department of Neurosurgery, Institute of ClinicalMedicine, Aalborg University Hospital, Denmark, c.bjarkam@rn.dk

3.b Authors' contributions

Study conception: Ryttersgaard, Johnsen, Riis, Mogensen & BjarkamReview: Ryttersgaard & Bjarkam
Data extraction and analysis: Ryttersgaard & Johnsen.
Drafting of manuscript: Ryttersgaard & Bjarkam
Critical revision: Ryttersgaard, Johnsen, Riis, Mogensen & Bjarkam

4. Amendments

The including criteria for age has been revised. As no identified studies had the chosen age rangeof 15-30 years the including criteria was changed to 13-35 years old.

No further changes were made

5. Support

No financial or other support is provided by a sponsor or founder

Introduction

6. Rationale

In 2012, the Ministry of Health and Elderly in Denmark founded the national project *'National studyon young brain injury survivors'* to improve rehabilitation for young brain injury survivors age 15-30years. The specific age group was among other things chosen because adolescence and young adulthood are described as vulnerable age periods with many transitions and increasing demandsfor independency (Meeus, 2016). The project encouraged us to identify the existing knowledge about prevalence of depression after moderate to severe TBI.

Although most patients with TBI are adolescents and young adults, studies on depression after TBIprimarily focus on adults in general (Guillamondegui et al., 2011; Osborn, Mathias, & Fairweather- Schmidt, 2014; Reekum, Cohen, & Wong, 2000; Sasse et al., 2014). Reported estimates of the prevalence of depression after TBI among adults varies substantially from approximately 5.3% (Koponen, Taiminen, Hiekkanen, & Tenovuo, 2011) to as high as 76.6% (Varney, Martzke, & Roberts, 1987). The identified reviews include studies on children or adults, and a review which investigate adolescents and young adults has not been identified. Pooled prevalence estimates of depression among adults with TBI vary from 17% in the first year after TBI to 43% in the long-term (Scholten et al., 2016). In relation to children and adolescents aged 0-18-years estimates of depression prevalence have been reported to be between 5.3% and 36% (Laliberté Durish, Pereverseff, & Yeates, 2017).

7. Objectives

The aim of the current systematic literature review is to identify the existing knowledge about the prevalence of depression after moderate to severe TBI in adolescents and young adults age 15-30years.

The aim of the study is not to evaluate an intervention, why the research question does not containthis. Comparators will be included in the discussion. This is further described in the Eligibility criteria (please see #8).

Methods

8. Eligibility criteria

The following description of participants, interventions, comparators and outcome underlie thesearch criteria as well as inclusion and exclusion criteria.

Participants: Adolescents and young adults with a moderate to severe TBI age 15-30 years at thetime of the injury. *Revision: None of the identified studies had a study cohort age of 15-30 years and we decided to include studies with an age range of 13-35 years.*
A study can be included although the study population include younger or older participant if datafor either the whole age group or part of it can be extracted.
A moderate to severe TBI is defined as 1) an acute GCS<13, and 2) an acute GCS>12 with an abnormal computed tomography (CT) scan of cerebrum. Acute GCS>12 and an abnormal CT-scanof cerebrum are in the literature referred to as complicated mild TBI and is included as studies have shown that sequelae after complicated mild TBI resembles sequelae after moderate TBI (Kashluba, Hanks, Casey, & Millis, 2008). Studies will also be included if the authors describe the study population as having a moderate to severe TBI, although the definition of severity of the injury is not described in the article.

Interventions: The review has not the purpose to evaluate an intervention. Intervention studies willnot be included, as it could affect the prevalence proportion of depression because intervention studies recruit a specific group of participants who needs an intervention.

Comparators: A comparison group is not required for a study to be included.

Outcome: The outcome is prevalence proportion of depression. A wide definition of depression is chosen to ensure that all possible studies are identified. Depression include depression diagnosedby a structured clinical interview as well as clinically significant depressive symptoms identified by a self-report questionnaire with a cut-off score (for further description please see #13).

9. Information sources

The search will be conducted in the electronic databases: PubMed, Embase, Cochrane and PsychInfo. The search will be conducted primo 2018, and will be updated later on if necessary. Furthermore, we will go through reference lists in included studies and relevant reviews.
Contact to authors, search in trail registers or other grey literature sources will not be included.

10. Search strategy

The search strategy is developed with a librarian and search specialist from Aalborg University Hospital. The search will include thesaurus terms and text words in the three themes: 1) TraumaticBrain Injury, 2) Depression and 3) Adolescents and young adults. Inside a theme the thesaurus terms and text words are separated with an OR, and themes are separated with an AND
Table 1 shows the draft for the search strategy in PubMed.

Table 1: Search strategy in PubMed

Traumatic Brain Injury	**Depression**	**Age**
Brain Injuries [Mesh]	Depressive Disorder [Mesh] Depression [Mesh]	Adolescent [MESH] Young Adult [MESH]
traumatic brain injur*	depressi*	Adolescen*
brain contus*		Young adult*
traumatic brain hemorrhag*		Youngster*
diffuse axonal		
diffuse brain injur*		

11. Study records

11a. Data management

The search records from all four databases will be imported to Refworks to identify duplets. Afterwards, the remaining records will be transferred to Covidence were the selection process willbe conducted.

11b. Selection process

The first author has the primary responsibility for screening process. First, all titles and abstracts will be screened for obviously irrelevant citations. After the initial screening all remaining records will be screened according to title, abstract and full-text. Records evaluated as eligible for inclusionand records with doubt about eligible will be discussed with the fifth author.

11c Data collection process

The first and second author will make the extraction of the data.

Authors of the included studies will not be contacted to get a confirmation of the extracted data.

12. Data items

Data extracted will include the following summary data: study design, sample characteristics,sample size and outcomes, which is exemplified below.

The following data will be extracted if available:
Study design
Country
Study location
Severity of the brain injury
Size of the population
Distribution of gender
Age (mean, SD and range)
Time-since-injury (mean, SD and range)
In- and exclusion criteria

Assessment tool for evaluating depression or depressive symptoms
Prevalence proportion of depression/clinically significant depressive symptoms (please refer #13)

13. Outcomes and prioritization

The outcome for this review is depression. To ensure that all relevant studies are included we usea broad definition of depression including both depression diagnosed by DSM-IV or ICD-10 and clinically significant depressive symptoms.

According to DSM-IV and ICD-10 depression is defined as major depressive episode (DSM-IV), minor depressive episode (DSM-IV) (*Diagnostic and statistical manual of mental disorders : DSM-IV*, 1995) and depressive episode (*ICD-10 : International statistical classification of diseases and related health problems*, 2016). Depression is often diagnosed by a diagnostic interview.
Many international studies use a self-report questionnaire to identify the degree of depressive symptoms. Most self-report questionnaires use a cut-off score to evaluate clinically significant depressive symptoms, which indicate a caseness of depression, as the person report a degree ofdepressive symptoms, which influence their daily living. Although, participants with clinically significant depressive symptoms may not full-fil the diagnostic criteria for depression, it is considered that significant knowledge will be lost if those studies are excluded.

14. Risk of bias in individual studies

Methods for risk of bias assessment is primarily developed to evaluate the study quality in intervention studies. The Newcastle-Ottawa Scale (NOS) is developed to evaluate quality of studies in review of observational studies, but the evaluation of the NOS is in progress, and for thatreason we did not include the method in this study. Furthermore, in epidemiology studies The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) is sometimes used, although it is not a tool to evaluate study quality (Da Costa, Cevallos, Altman, Rutjes, & Egger, 2011).

Based on this an applicable method for assessing risk of bias of the individual studies could not beidentified, and instead we have developed our own Risk of Bias Assessment based on a description from Agency of Health Research and Quality (AHRQ) (Viswanathan et al., 2014)

Risk of Bias was evaluated according to setting (selection bias), inclusion criteria (selection bias),recruitment process (selection bias), completeness (attrition bias), definition of TBI severity (detection bias), method to evaluate depression (detection bias) and report of outcome (reportingbias). The RoB will be evaluated as “Low risk”, “Unclear risk” and “High risk”. In table 2 you find the description of the selected bias’s

Table 2: Description of the Risk of Bias assessment

	Low risk	Unclear risk	High risk
Setting (selection bias)	Multi-centre study	Unclear whether it is a single-centre or multi-centre study	Single-centre study
Inclusion criteria (selection bias)	Inclusion and exclusion criteria are well-described	Either inclusion or exclusion criteria is not described	Inclusion and exclusion criteria are not described
Recruitment process (selection bias)	The recruitment process is well-described	The recruitment process is described but unclear	The recruitment process is notdescribed or there hasbeen a selection in the subjects contacted
Completeness (attrition bias)	Attrition is reported and it is analysed whether the included subjects differ from the non-participants	There is uncertainty about the reported attrition and the analysis of the two groups.	Attrition is not reportedand/or not analysed.
Definition of TBI severity (detectionbias)	The definition of TBI severity is well-described and corresponds to the included participants	The definition of TBI severity is not described, but data on GCS, PTA, coma length or results from CT-/MR-scan are available in the text	The definition of TBI severity is not described
Method to evaluate depression/depressive symptoms (detection bias)	Structured interview with description of diagnostic method	Structured interview without description ofdiagnostic method	Self-eport questionnaire
Report of outcome (reporting bias)	The relevant results are reported	The relevant results are reported, but descriptive data or attrition analysis is missing	The relevant results are not reported.

15. Data synthesis

A pooled prevalence proportion of depression will be calculated if the risk of bias assessment shows that the included studies have a high quality and the results from the included studies canbe generalized to the general population of adolescents and young adults with a moderate to severe TBI.
No further analysis will be made.

If a pooled prevalence proportion cannot be calculated the prevalence proportions from theincluded studies will be presented.

16. Meta-bias(es)

Assessment of meta-bias(es) are not planned

17. Confidence in cumulative evidence

Due to the fact that this review only focus on prevalence proportion and not effect of interventionsan assessment of the strength of the evidence is not relevant.

References

Da Costa, B. R., Cevallos, M., Altman, D. G., Rutjes, A. W. S., & Egger, M. (2011). Uses andmisuses of the STROBE statement: Bibliographic study. *BMJ Open*, *1*(1), 1–6. https://doi.org/10.1136/bmjopen-2010-000048

Diagnostic and statistical manual of mental disorders : DSM-IV (4ed ed.). (1995). AmericanPsychiatric Association.

Guillamondegui, O., Montgomery, S., Phibbs, F., McPheeters, M., Alexander, P., Jerome, R., …KE., H. (2011). *Traumatic Brain Injury and Depression. Comparativ Effectiveness Review number 25*. Agency for Healthcare Research and Quality.

ICD-10 : International statistical classification of diseases and related health problems (2016th ed.).(2016). World Health Organization.

Kashluba, S., Hanks, R. A., Casey, J. E., & Millis, S. R. (2008). Neuropsychologic and functionaloutcome after complicated mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *89*(5), 904–911.

Koponen, S., Taiminen, T., Hiekkanen, H., & Tenovuo, O. (2011). Axis I and II psychiatric disordersin patients with traumatic brain injury: A 12-month follow-up study. *Brain Injury*, *25*(11), 1029– 1034.

Laliberté Durish, C., Pereverseff, R. S., & Yeates, K. O. (2017). Depression and depressive symptoms in pediatric traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *33*(3),E18–E30.

Meeus, W. (2016). Adolescent psychosocial development: A review of longitudinal models andresearch. *Developmental Psychology*, *52*(12), 1969–1993.

Osborn, A. J., Mathias, J. L., & Fairweather-Schmidt, A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews*, *47*, 1–15.

Reekum, R. van, Cohen, T., & Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(3), 316–327.https://doi.org/10.1053/scnp.2000.9555

Sasse, N., Gibbons, H., Wilson, L., Martinez, R., Sehmisch, S., Von Wild, K., & Von Steinbüchel, N. (2014). Coping strategies in individuals after traumatic brain injury: Associations with health-related quality of life. *Disability and Rehabilitation*.https://doi.org/10.3109/09638288.2014.893029

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F., & Polinder, S. (2016). Prevalence of and risk factors for anxiety and depressive disorders after traumatic braininjury: A systematic review. *Journal of Neurotrauma*, *33*(22), 1969–1994. https://doi.org/10.1089/neu.2015.4252

Varney, N. R., Martzke, J. S., & Roberts, R. J. (1987). Major depression in patients with closedhead injury. *Neuropsychology*, *1*(1), 7–9.

Appendix C. Paper II

Depression and cognitive sequelae registered within the first year among young Danish TBI survivors

Ryttersgaard TO[a,d], Riis JØ[b], Johnsen SP[c], Mogensen PH[a], Bjarkam CR[b,d].

Scandinavian Journal of Psychology, 2020, 61(5), p. 663-670.

Affiliations:

a) Department of Neurology, Aalborg University Hospital, Aalborg, Denmark

b) Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark

c) Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark

d) Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Scandinavian Journal of Psychology, 2020, 61, 663–670 DOI: 10.1111/sjop.12660

Health and Disability

Depression and cognitive sequelae registered within the first year among young Danish TBI survivors

TRINE OKKERSTRØM RYTTERSGAARD[1] JENS ØSTERGAARD RIIS,[2] SØREN PAASKE JOHNSEN,[3] POUL HENNING MOGENSEN[4] and CARSTEN REIDIES BJARKAM[5]

[1]*Department of Neurology, Institute of Clinical Medicine, Aalborg University Hospital, Ladegårdsgade 5, 7th, Aalborg, 9000, Denmark*
[2]*Department of Neurosurgery, Aalborg University Hospital, Hobrovej 18, Aalborg, 9000, Denmark*
[3]*Danish Center for Clinical Health Services Research, Institute of Clinical Medicine, Aalborg University and Aalborg University Hospital, Mølleparkvej 10, Aalborg, 9000, Denmark*
[4]*Department of Neurology, Aalborg University Hospital, Ladegårdsgade 5, 7th, Aalborg, 9000, Denmark*
[5]*Department of Neurosurgery, Institute of Clinical Medicine, Aalborg University Hospital, Hobrovej 18, Aalborg, 9000, Denmark*

Ryttersgaard, T. O., Riis, J. Ø., Johnsen, S. P., Mogensen, P. H. & Bjarkam, C. R. (2020). Depression and cognitive sequelae registered within the first year among young Danish TBI survivors. *Scandinavian Journal of Psychology, 61,* 663–670.

The aim of the study was to determine the proportion of depression and cognitive sequelae among young (15-30 years) Danish TBI survivors referred to interdisciplinary evaluation through a nationwide government-initiated health initiative. The cross-sectional study is based on data from the "Danish register for young adults with acquired brain injury" on TBI survivors included from October 2013 to December 2016. The main measures were Major depression inventory, Trail making test A and B, Fluency, Word learning with selective reminding, Matrix reasoning, Coding and Glasgow outcome scale - extended (GOS-E). During the study period, 131 young TBI survivors were referred to one of five national outpatient clinics. Ninety-six had complete data and of these 14.6% fulfilled the ICD-10 diagnostic criteria for depression and 34.4% had cognitive sequelae. An association was found between depression and cognitive sequelae ($p = 0.004$). Patients with both depression and cognitive sequelae (n = 10) had a significantly lower mean score on GOS-E ($p = 0.0001$). Depression and cognitive sequelae were frequent and associated with a poorer global functional outcome among young TBI survivors referred within a year after trauma. This finding and the notion that only 20% of the expected TBI population was referred to this nationwide health initiative indicate an unacknowledged need for interdisciplinary follow-up.

Key words: Adolescents, cognitive sequelae, depression, global functional outcome, governmental health initiative, traumatic brain injury.

Trine Okkerstrøm Ryttersgaard, Department of Neurology, Aalborg University Hospital, Aalborg, Denmark. E-mail: try@rn.dk

INTRODUCTION

Traumatic brain injury (TBI) may result in physical, cognitive, behavioural and/or emotional deficits affecting the functional outcome and quality of life (Gorgoraptis, Zaw-Linn, Feeney *et al*., 2019; Griffen & Hanks, 2014; Marsh, 2019; Stenberg, Godbolt, Nygren, De Boussard, Levi & Stålnacke, 2015). In Denmark, the incidence of severe head trauma causing moderate to severe TBI is approximately 2.5/10,000 for adolescents and young adults, equaling 200–250 cases a year (Danish Health Authority, 1997). This group might be more vulnerable towards the consequences of emotional and cognitive sequelae after TBI/acquired brain injury (ABI) as adolescence and young adulthood are life periods with many transitions such as becoming independent, finding a peer group and dealing with school shifts (Meeus, 2016). To accommodate this The Danish Ministry of Health founded the national project "National study on young brain injury survivors" in 2012, to provide a nationwide outpatient service to young ABI survivors; Consequently, one outpatient clinic was established in every of the five Danish Health Regions. In relation to the project, the Danish Clinical Quality Database "Danish register for young adults with acquired brain injury" (Danish acronym DRUE) was created (Nørgaard & Johnsen, 2016; Sørensen, Pedersen, Jørgensen & Ehrenstein, 2016; Svendsen & Ingeman, 2017). DRUE consists of data on 15–30-year-old Danes with an ABI who were referred to one of the five outpatient clinics from October 2013 to August 2017 (Svendsen & Ingeman, 2017).

The literature about depression and cognitive sequelae among adolescents and young adults with moderate to severe TBI are sparse. Studies on depression among young survivors of moderate to severe TBI show a wide variation of depression with prevalence proportions of 1.3%–60% (Bombardier, Fann, Temkin, Esselman, Barber & Dikmen, 2010; Garske & Thomas, 1992; O'Connor, Zatzick, Wang *et al*., 2012; Poggi, Liscio, Adduci *et al*., 2003; Tyerman & Humphrey, 1984; van Reekum *et al*., 1996; Willmott *et al*., 2015). The variation could be due to study quality, but might also indicate that young survivors of moderate to severe TBI are in higher risk of being diagnosed with depression compared to the general population of adolescents and young adults (Ryttersgaard, Johnsen, Riis, Mogensen & Bjarkam, 2020).

Accordingly, to test our hypotheses: (1) that there is an association between depression and cognitive sequelae in young TBI survivors; and (2) that young TBI survivors with depression and/or cognitive sequelae have a lower global functional outcome; the aims of the present study were to:

1. Determine the proportion of depression and cognitive sequelae among young (age 15–30 years) Danish TBI survivors referred to one of the five outpatient clinics less than a year after the injury.
2. Examine whether an association between depression and cognitive sequelae existed in the generated cohort.

3. Examine how depression and cognitive sequelae were associated with global functional outcome classified by GOS-E.

Thus, this is the first study about depression and cognitive sequelae among young survivors of TBI based on data from a government-initiated nationwide health project in a Scandinavian country. In addition, to the best of the authors' knowledge it is the first study to examine whether depression, cognitive sequelae and global functional outcome are associated among young TBI survivors less than a year after an intracranial brain injury.

METHOD

Population

The DRUE-TBI cohort was defined as the patients in DRUE with a traumatic brain diagnostic code (International Classification of Diseases – 10th revision, S06.1-S06.9) (c.f. Table 1), which in the period October 2013 to December 2016 were referred to one of the five established outpatient clinics and invited to an interdisciplinary examination less than a year after the TBI. For non-attendees the date of visitation was used for identification.

The identification was based on the diagnosis given by the medical doctor after the first interdisciplinary examination. The diagnosis T90.5 (late effects of TBI), which also enabled DRUE inclusion, was mistakenly assigned to three patients although they were examined within a year after their TBI. These patients are therefore included in our cohort. For non-attendees the referral diagnostic group were used for identification. The traumatic brain diagnostic codes were chosen as inclusion criteria as information about acute Glasgow Coma Score (GCS) or Posttraumatic Amnesia (PTA) were not registered in DRUE.

Patients with skull fracture or facial fractures without intracranial lesions were excluded from this study. Patients with mild TBI including concussion were not included in DRUE (Svendsen & Ingeman, 2017).

Patients were referred to an interdisciplinary examination at the outpatient clinics from hospital departments, medical specialists or general practitioners if they had been admitted to hospital with an ABI (incl. TBI) or had an unmet need for rehabilitation because of an ABI earlier in life. In two of the five outpatient clinics patients could also be referred by the municipality.

Patients in the DRUE-TBI cohort were included in the statistical analysis if they had complete data on MDI, the eight neuropsychological tests and GOS-E.

Table 1. *ICD-10 diagnostic codes for the DRUE-TBI category*

Primary diagnostic code	Description
S061	Traumatic cerebral edema
S062	Diffuse traumatic brain injury
S063	Focal traumatic brain injury
S064	Epidural hemorrhage
S065	Traumatic subdural hemorrhage
S066	Traumatic subarachnoid hemorrhage
S067	Traumatic intracranial injury with protracted coma*
S068	Other specified intracranial injuries
S069	Unspecified intracranial injury
T905	Sequelae after intracranial injury*

Notes: Patients with skull fracture or facial fractures without intracranial lesions were excluded from this study.
*Translated from Danish, as they are not part of ICD-10.

Measurements

Demographics. Information on gender, age at injury, age at first visit and time-since-injury was available in DRUE.

Depression. Major depression inventory (MDI) was used to determine the prevalence of depression in the sample and to investigate whether there was an association between depression and cognitive sequelae (Bech, Rasmussen, Olsen, Noerholm & Abildgaard, 2001; Bech, Timmerby, Martiny, Lunde & Soendergaard, 2015; Olsen, Jensen, Noerholm, Martiny & Bech, 2003).

MDI is a self-rating inventory developed to measure depression by the patients' self-reported symptoms. It consists of 12 symptom questions scored on a five-point Likert scale: All the time, Most of the time, Slightly more than half the time, Slightly less than half the time, Some of the time, or At no time.

MDI can be used as a diagnostic instrument by using algorithms leading to either depression (mild, moderate or severe) according to ICD-10 (World Health Organization, 2016) or major depression disorder defined by DSM-IV (American Psychiatric Association, 1995). In this study, the ICD-10 algorithm was used, as only the core symptoms, accompanying symptoms and the total score were registered in DRUE. The ICD-10 diagnostic criteria for depression request the presence of minimum two core symptoms "Most of the time" and two accompany symptoms "Slightly more than half of the time" (World Health Organization, 2016) (cf. Supplementary 1).

The sensitivity and specificity of the MDI have been assessed in a group of subjects with depressive symptoms, which showed a sensitivity between 0.86 and 0.92 and a specificity between 0.82 and 0.86 (Bech *et al.*, 2001). The sensitivity and specificity have not been assessed in a group of TBI patients. Consequently, the total score of MDI was not used as a continuous variable, as the symptoms reported also could reflect cognitive sequelae or fatigue (Dornonville de la Cour, Forchhammer, Mogensen & Norup, 2018).

Cognitive sequelae – neuropsychological examination. Cognitive sequelae were assessed through a neuropsychological examination conducted by neuropsychologists at the five outpatient clinics.

Trail Making Test A (TMT-A), Trail Making Test B (TMT-B) and Coding were used to measure processing speed. TMT-A measures simple processing speed and TMT-B measures processing speed and divided attention, for both tests the time in seconds was registered (Reitan, 1992). Coding is a subtest in Wechsler Adult Intelligence Scale IV (WAIS-IV) in which the number of correctly copied symbols (0–135) within 120 seconds was registered (Wechsler, 2011).

Word learning with selective reminding am. Buschke was used to measure verbal learning and memory (Buschke & Fuld, 1974). The Danish version consists of ten unrelated words with up to ten learning trials and a recall after 10 minutes. The learning score was the number of failures subtracted from 100 and the memory score was the number of correct recalled words after 10 minutes.

Fluency – category and letter were used to measure fluency (Strauss, Sherman & Spreen). The examinee had to mobilize as many animals and S-words as possible in 60 seconds, respectively. The total number of correctly mobilized words was registered for each trial.

Matrix reasoning measures perceptual reasoning and is a subtest in WAIS-IV (Wechsler, 2011). The total number of correct answers (0–26) were registered.

For TMT-A and TMT-B a low score indicates a better cognitive performance while a high score indicates a better cognitive performance for Coding, Word learning with selective reminding, Fluency and Matrix reasoning. Patients were registered as "Could not complete" if the neuropsychologist judged that the non-completion was due to cognitive sequelae.

Cognitive sequelae were defined as minimum two performances 2 SD below the mean for the best available Danish population-based norms (Jørgensen, 2012; Wechsler, 2011) and/or registrations as "Could not complete". This definition was chosen to avoid a mistaken interpretation of one performance below 2 SD, as the performance could have occurred as a coincidence. The age group 20–29 was chosen as reference group for

TMT-A and TMT-B, Fluency and Word learning with selective reminding (Jørgensen, 2012), while the age group 20–24 was chosen for Matrix reasoning and Coding (Wechsler, 2011).

Global functional outcome. The Glasgow outcome scale – extended (GOS-E) was used to classify the patients' overall outcome (Hudak, Caesar, Frol *et al*., 2005; Wilson, Pettigrew & Teasdale, 1998). GOS-E is a structured interview based outcome scale, which divides functional outcome into eight categories: Dead, Vegetative state, Lower severe disability, Upper severe disability, Lower moderate disability, Upper moderate disability, Lower good recovery, and Upper good recovery, equaling a score from one to eight.

The interview was conducted by occupational therapists at the five outpatient clinics. Blinding of the occupational therapist to other relevant study measures are not described in the description of DRUE. Inter-rater reliability has not been assessed.

Statistical analysis

Checking for normality showed that the continuous descriptive data were not normally distributed and non-parametric tests were used when suitable. As the study sample is relatively small a descriptive assessment of whether the included patients differed from patients without complete data and non-attendees was conducted.

Prevalence proportion of depression and cognitive sequelae in the study population was calculated with 95% CI. The finite population correction factor (FPC) was investigated but not used, as it almost equalled 1 (FPC = 0.93) and only had a little impact on CI. The one-sample test of proportion was used to evaluate whether the proportion of cognitive sequelae in the study population differed from the expected (normal distribution based) proportion (2.2%) among Danish adolescents and young adults (age 15–30). Fisher's exact test was used to examine whether there was an association between depression and cognitive sequelae. A Two-sample Wilcoxon rank sum was used to examine whether the performance on the neuropsychological tests differentiated between the depressed group and the non-depressed group. For this analysis patients registered as "Could not complete" on a neuropsychological test were given a score one worse than the worst performance in the study population. This seems applicable as a patient was registered as "Could not complete" if the neuropsychologist evaluated that the patient could not complete the test due to cognitive sequelae and thus these must be the patients with the most severe cognitive sequelae (Dikmen, Machamer, Winn & Temkin, 1995).

Finally, a two-sample Wilcoxon rank sum was used to examine whether the global functional outcome among subjects with depression and/or cognitive sequelae, differed from the subjects without depression and cognitive sequelae.

All analyses used a two-tailed significance level of $p < 0.05$. Data were analysed using Stata, version 15.0 (StataCorp, 2017).

RESULTS

During the period October 2013 to December 2016, 131 young TBI survivors were referred to one of the five Danish outpatient clinics and invited to an interdisciplinary examination within a year after the TBI. Of the 131 patients, 96 (73.3%) had complete data on the MDI, the eight neuropsychological tests and the GOS-E. Thus 35 were excluded from further analysis due to non-attendance (n = 12, 9.1%) and incomplete data (n = 23, 17.6%). Characteristics are shown in Table 2.

Table 2. *Descriptive data for included and excluded patients*

	Included patients with complete data (N = 96)	Patients without complete data (N = 23)	Patients without 1st outpatient visit (N = 12)
Mean age at injury (SD)	22.6 (4.2)	22.0 (4.8)	21.5 (3.3)
Male (%)	71 (73.9)	17 (73.9)	8 (66.7)
Mean days from injury to first visit (SD)	170.8 (88.1)	160.3 (110.9)	
Mean age at 1. visit (SD)	23.1 (4.2)	22.5 (4.6)	
Diagnostic codes			
S06.1	1%		
S06.2	27.1%	34.8%	
S06.3	21.9%	13%	
S06.4	4.2%	8.7%	
S06.5	16.7%	21.7%	
S06.6	16.7%	4.4%	
S06.7			
S06.8	8.3%	4.4%	
S06.9	1%		
T90.5	3.1%	13%	
Lenght of education	N = 94	N = 19	
No education	1.1%		
Primary School	45.7%	68.4%	
High school graduation	18%	31.6%	
Vocational education/training	20.2%		
Short advanced	2.1%		
Medium long advanced	5.3%		
Long advanced	3.2%		
Work before the TBI	N = 94	N = 20	
Education/Military duty	52.1%	65%	
Work, normal condition	34%	26.6%	
Work, special conditions/Disability pension	2.1%	0.1%	
Unemployed	11.7%		
Complete GOS-E N (%)	96 (100)	14 (60.9)	
GOS-E (SD)	5.7 (1.3)	5.6 (1.7)	

The patients included were primarily males (n = 71, 74.0%), with a mean age of 23.1 years (SD: 4.24, range: 15.3–31.1) at the first visit, which took place on average 170.8 days (SD: 88.1, range: 20–365) after injury. The included and excluded patients resemble each other according to age at injury, gender, age at first visit, time-since-injury and GOS-E score. Length of education among the included patients resembles the length of education in the normal population of Danish adolescents and young adults (Statistics Denmark, 2015, cf. Supplementary 2).

Prevalence of depression and cognitive sequelae

Among the 96 included subjects, 14.6% (95% CI: 8.2–23.3) fulfilled the ICD-10 criteria for depression. Cognitive sequelae were noted among 34.4% (95% CI: 25.0–44.8) of the study population, which differs vastly from the expected 2.2% in the general population ($z = 21.49$, $p < 0.0001$). Depression and cognitive sequelae were equally distributed among patients with intracranial injury (S06.1; S06.2; S06.3; S06.7; S06.8; S06.9) and patients with hemorrhage (S06.4; S06.5, S06.6) (cf. Supplementary 3).

Table 3, shows the proportion of patients who on the neuropsychological test performed in the ranges no impairment, borderline and impaired, as well as the patients who could not complete the specified cognitive test due to cognitive dysfunction. Thus the proportion of impaired performance (incl. patients who could not complete the test due to cognitive difficulties) on the neuropsychological tests varied from 7.3% (95% CI: 3.0–14.4) to 29.2% (95% CI: 20.3–39.3).

Four groups could be identified based on depression and cognitive sequelae: (1) Patients with depression and cognitive sequelae (n = 10); (2) Patients with cognitive sequelae (n = 23); (3) Patients with depression (n = 4); and (4) Patients without depression and cognitive sequelae (n = 59).

Table 3. *Prevalence and severity of cognitive impairment (n = 96)*

	Classification level			
Neuropsychological test	No impairment	Borderline	Impaired	Could not complete
Trail making test A	85%	3%	10%	1%
Trail making test B	64%	6%	26%	4%
Coding WAIS-IV	84%	8%	3%	4%
Selective reminding - learning	65%	7%	19%	9%
Selective reminding - memory	75%	0	16%	9%
Fluency – category	75%	16%	7%	2%
Fluency – letter	84%	7%	6%	2%
Matrix reasoning WAIS-IV	89%	4%	6%	1%

Notes: No impairment: A performance better than 1.5 SD below the mean for the best available Danish population-based norms. Borderline: A performance 1.5-2 SD below the mean for the best available Danish population-based norms. Impaired: A performance more than 2 SD below the mean for the best available Danish population-based norms. Could not complete: Patients who could not complete the test due to cognitive sequelae.

Table 4. *Comparison of the neuropsychological performances in the depressed group versus the non-depressed group*

Neuropsychological test	Non-depressed N = 82	Depressed N = 14	z	p-value
Trail Making A	30.6 (12.5)	40 (19.4)	−2.556	0.0106*
Could not complete	0/82	1/14		
Trail Making B	79.4 (36.2)	138.4 (71.2)	−3.115	0.0018**
Could not complete	1/82	3/14		
Coding WAIS-IV	58.6 (14.84)	42.4 (20.41)	2.977	0.0029**
Could not complete	1/82	3/14		
Selective reminding – learning	82.8 (14.6)	65.7 (23.1)	2.619	0.0088**
Could not complete	4/82	5/14		
Selective reminding – memory	8.1 (2.2)	5.4 (3.1)	3.262	0.0011**
Could not complete	4/82	5/14		
Fluency – category	20.6 (5.6)	17.3 (6.3)	2.045	0.0409*
Could not complete	1/82	1/14		
Fluency – letter	11.4 (4.6)	11.4 (4.1)	−0.057	0.9544
Could not complete	1/82	1/14		
Matrix reasoning	17.8 (4.0)	14.2 (4.5)	2.923	0.0035**
Could not complete	0/82	1/14		

Notes: Patients registered as "Could not complete" were assigned a score one worse than the worst score in the study population (cf. Statistical analysis).
*$p < 0.05$
**$p < 0.01$
[Correction made on 8 July 2020, after first online publication: "Could not complete" values in Table 4 have been updated in this version.]

Association between depression and cognitive sequelae

An association was found between depression and cognitive sequelae (p = 0.004).

Table 4, show the mean and SD for each of the neuropsychological tests for the depressed group (n = 14) versus the non-depressed group (n = 82), respectively. A significant difference was found on seven of the eight neuropsychological tests with the depressed group having a mean indicating a worse performance than the non-depressed group. A clinical significant difference was found on TMT-B as well as Word learning with selective reminding – learning and memory with the depressed group having a mean score more than 2 SD below the mean for the non-depressed group.

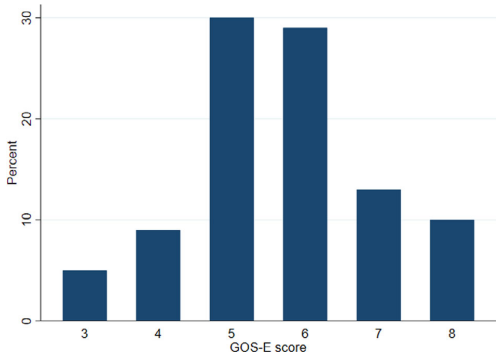

Fig. 1. Distribution of GOS-E score (n = 96). [Colour figure can be viewed at wileyonlinelibrary.com]

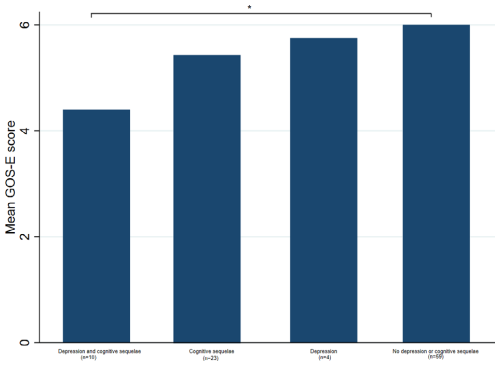

Fig. 2. Mean GOS-E score for the four groups. *p = 0.0001 [Colour figure can be viewed at wileyonlinelibrary.com]

Global functional outcome and association with depression and cognitive sequelae

The majority had a GOS-E score of 5 or 6 (61.5%, 95% CI: 51.0–71.2) indicating moderate disabilities with affected functional level in relation to work/education and independent life. Only 24.0% (95% CI: 15.8–33.7) of the study population had a GOS-E score of 7 or 8 indicating a good recovery, equaling a resumption of normal life with return to work/education. The distribution of the GOS-E score is shown in Figure 1.

Figure 2, shows the mean GOS-E score for the four patient groups, with the highest mean GOS-E score being 6. The absolute mean difference on GOS-E between patients with depression and cognitive sequelae and patients without depression and cognitive sequelae was 1.6 (95% CI: 0.8–2.4, z = 3.987, p = 0.0001), with patients with depression and cognitive sequelae having the lowest mean GOS-E score. Patients with depression or cognitive sequelae had a mean GOS-E score positioned between patients with depression and cognitive sequelae and patients without depression and cognitive sequelae with an absolute mean difference on 0.25 (95% CI: –1.0.-1.5, z = 0.483, p = 0.6294) and 0.57 (95% CI: –0.05–1.18, z = 0.1.563, p = 0.1181), respectively.

DISCUSSION

In this study, almost one in six if the young TBI survivors referred to the "National study on young brain injury survivors" within a year after trauma fulfilled the ICD-10 diagnostic criteria for depression and more than 1/3 had cognitive sequelae. The global functional outcome was generally affected in the study population, as only 24.0% reported a functional outcome with minor disabilities affecting daily life. Patients with both depression and cognitive sequelae had a significantly poorer global functional outcome compared to patients without depression and cognitive sequelae.

As GCS and PTA at hospital admission were not registered in DRUE ICD-10 traumatic brain diagnostic codes (S06.1-S06.9) were used as an inclusion criterion (Table 1). The traumatic brain diagnostic codes correspond to an intracranial traumatic brain lesion or diffuse axonal damage. The patients included in the study seem to resemble patients with moderate to severe TBI, as studies have shown that neuropsychological and functional outcome of patients with complicated mild TBI (GCS>12 and intracranial lesion) is similar to the outcome of patients with moderate TBI (Griffen & Hanks, 2014; Kashluba, Hanks, Casey & Millis, 2008). Consequently, the results of this study will be compared to the existing literature on adolescents and young adults with moderate to severe TBI.

The proportion of impaired performances on specific neuropsychological tests varied from 7–29%, which are consistent with the existing literature (Kersel, Marsh, Havill & Sleigh, 2001; Marsh, 2019) and support the fact that cognitive sequelae after moderate to severe TBI are common but heterogeneous. Cognitive sequelae were defined, as minimum two performances 2 SD below the mean for Danish population-based norms or "Could not complete" to decrease the probability to overinterpret one coincidental impaired performance. Consequently, our definition might lead to an underestimation of the prevalence of cognitive sequelae, as 16 subjects with one impaired performance were evaluated as not having cognitive sequelae. This notion could be supported by the fact that the general functional outcome was affected among 76% of the study population. Contrarily, the global functional outcome is affected by other factors than cognitive and emotional sequelae, as for example physical sequelae and fatigue are common sequelae after TBI (Ponsford, Downing, Olver *et al.*, 2014). In addition, the combination of the neuropsychological tests in DRUE covers most of the cognitive domains with two neuropsychological tests and more than one impaired performance can be expected if a patient has cognitive sequelae. In conclusion, it seems reasonable to applicate the definition and decrease the possibility to overinterpret one impaired performance.

As hypothesized, the study found an association between depression and cognitive sequelae with the depressed group having a significantly worse performance than the non-depressed group, especially according to TMT-B and Word learning with selective reminding (learning and memory). This result is consistent with the results of Stenberg *et al*. (2015), who found a negative relationship between the cognitive performance and the depression score among adults with severe TBI, as well as the results of Hart, Brenner, L., Clark *et al*. (2011) who found an association between depression and cognitive performance among adults with moderate to severe TBI. On the other hand, Satz, Forney, Zaucha *et al*. (1998) did not find an association between depression status and the performance on the neuropsychological tests 6 months after moderate to severe TBI, which could indicate that time-since-injury might influence the association between depression and cognitive sequelae.

The prevalence of depression was lower than reported in most of the existing literature on depression among young survivors of moderate to severe TBI (Ryttersgaard *et al*., 2020). The use of different assessment methods and the differences between ICD-10 and DSM-IV diagnostic criteria could be one explanation (Osborn, Mathia & Fairweather-Schmidt, 2014). The difference could also be caused by the fact that most studies report the prevalence of clinically significant depressive symptoms, which in most cases do not resemble the diagnostic criteria for depression (Osborn *et al*., 2014; Ryttersgaard *et al*., 2020; Seel, MacCiocchi & Kreutzer). Furthermore, the difference could also be related to the fact that depression might increase with time-since-injury, as shown in studies on adults (Scholten *et al*., 2016) or might be due to the fact that DRUE used traumatic brain diagnostic codes

(Table 1) as an inclusion criterion instead of GCS score or PTA. In spite of this, the prevalence of depression was higher than reported in the general population of adolescents and young adults (Bruffaerts, Vilagut, Demyttebaere *et al*., 2009; World Health Organization, 2017), which is consistent with the existing literature on young survivors of moderate to severe TBI (Ryttersgaard *et al*., 2020). The result indicates that many young survivors of moderate to severe TBI struggle with emotional sequelae, which may further influence their functional outcome. This is supported by the fact that patients with both depression and cognitive sequelae had the lowest global functional outcome assessed with GOS-E (Figure 2). To the best of the authors' knowledge no studies have examined the relationship between depression, cognitive sequelae and global functional outcome, but studies in adults have shown an association between depression and GOS/GOS-E (Hart *et al*., 2011; Satz *et al*., 1998), which support the fact that depression influence the functional outcome level.

The participants in this study were identified through an extraordinary effort aimed at Danish adolescents and young adults with an ABI initiated by the Danish Ministry of Health in 2012. This study demonstrates that many of the referred adolescents and young adults with an intracranial brain lesion had cognitive and emotional sequelae, which affected their global functional outcome within a year after the injury. In the three-year study period, we would have expected approximately 600–750 new cases of adolescents and young adults with a structural CT or MRI verified traumatic brain lesion in Denmark. This means that only 20% of the potential cohort was referred to one of the outpatient clinics and registered in DRUE. The database cannot tell us the reason for the low registration, which could be due to ignorance about the initiative, as the outpatient clinics were placed in five hospitals, one in each of the five health regions, while TBI survivors are treated on several hospitals and after discharge affiliated at more than 3,000 general practitioners. The low registration could also be because referral for some of the young survivors was considered unnecessary. This might occur if the young survivor recovered well at the hospital, or if the young survivor had severe sequelae and was discharged from the hospital to the right rehabilitation setting or if the sequelae were invisible or unnoticed at the hospital. This could explain the low rate of patients with a GOS-E score equaling a good recovery compared to the existing literature (Einarsen, van der Naalt, Jacobs *et al*., 2018; Forslund, Perrin, Røe *et al*., 2019), as well as the low rate of patients with severe disability.

The study identifies a need for interdisciplinary outpatient clinics to examine cognitive and emotional sequelae within the first year after a moderate to severe TBI, as this affects the global functional outcome. The relatively low registration implicates a need to allocate attention to how young TBI survivors with psychological or cognitive sequelae are identified to ensure that no one is neglected. The results also implicate a need to focus on cognitive sequelae and depression as part of the rehabilitation process and it seems vital that young survivors of moderate to severe TBI are offered holistic rehabilitation programmes to ensure that they reach the best obtainable functional level.

Further studies are needed to examine how depression and cognitive sequelae are associated with each other and the global functional outcome. Moreover, it would be interesting to investigate how prevalence proportion of depression is associated with time-since-injury and whether adolescents and young adults differentiate from older adults according to the risk of developing depression after moderate to severe TBI. Finally, it would be beneficial to investigate why only 20% of the potential TBI population were referred to the outpatient clinics.

Study limitations

The study benefited from the possibility to use data from the Danish national clinical quality database DRUE, which ensured a multicentre study with representation of the whole of Denmark. The study also benefited from the fact that no differences were found between the included and excluded subjects and the fact that the education attainment among the included subjects resembled the Danish population of adolescents and young adults. A limitation of the study is that only 131 adolescents and young adults with traumatic brain lesion were registered in DRUE, which corresponds to 20% of the estimated potential cohort. This could be a selection bias, as the registration in DRUE is dependent on a referral to the outpatient clinics instead of a recruitment of participation at the acute hospital departments in Denmark. As discussed, the low registration could have several explanations, and consequently it could be that both patients without sequelae and patients with severe sequelae were not referred to the interdisciplinary examination. In addition, DRUE had a relatively low completeness of data with only 73.3% of the DRUE-TBI cohort having complete data on MDI, neuropsychological tests and GOS-E. Another limitation of the study is the use of a self-report questionnaire to detect depression instead of a clinical diagnostic interview, which could lead to information bias.

CONCLUSION

Depression and cognitive sequelae were frequent and associated with a poorer global functional outcome among young Danish TBI survivors sampled for the DRUE-initiative within a year after trauma. This finding and the notion that only 20% of the expected TBI population was referred to this national health initiative indicate an unacknowledged need for posttraumatic psychological and cognitive follow-up.

The authors want to acknowledge all young TBI survivors who have visited one of the five Danish outpatient clinics, all employees at the five outpatient clinics and the board members of DRUE for making this study possible. We also want acknowledge The Danish Clinical Registries (RKKP) for allowing us to use data from the national clinical registry 'Danish registry for young individuals with acquired brain injury' (Danish acronym DRUE: Dansk Register for Unge med Erhvervet hjerneskade). The authors also want to acknowledge Maja Søndergaard Worm who has done an extensive work as data manager for DRUE. Finally, the authors want to acknowledge Kristine Ahlmann Hjuler for her thorough language editing.

REFERENCES

American Psychiatric Association (1995). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington DC: American Psychiatric Association.

Bech, P., Rasmussen, N. A., Olsen, L. R., Noerholm, V. & Abildgaard, W. (2001). The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *Journal of Affective Disorders*, *66*, 159–164.

Bech, P., Timmerby, N., Martiny, K., Lunde, M. & Soendergaard, S. (2015). Psychometric evaluation of the Major Depression Inventory (MDI) as depression severity scale using the LEAD (Longitudinal Expert Assessment of All Data) as index of validity. *BMC Psychiatry*, *15*, 1–7.

Bombardier, C. H., Fann, J. R., Temkin, N. R., Esselman, P. C., Barber, J. & Dikmen, S. S. (2010). Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA*, *303*, 1938–1945.

Bruffaerts, R., Vilagut, G., Demyttebaere, K., Alonso, J., Barbaglia, G., Boyd, A. *et al.* (2009). *The burden of mental disorders in the European Union –the EU contribution to the World Mental Health Surveys Initiative*. Retrieved 30 August 2019 from http://www.eu-wmh.org/

Buschke, H. & Fuld, P. (1974). Evaluating storage, retention and retrieval in disordered memory and learning. *Neurology*, *24*, 1019–1025.

Danish Health Authority (1997). *Behandling af traumatiske hjerneskader og tilgrænsende lidelser* [Treatment of traumatic brain injury and similar diseases]. Copenhagen: Danish Health Authority.

Dikmen, S. S., Machamer, J. E., Winn, H. R. & Temkin, N. R. (1995). Neuropsychological outcome at 1-year post head injury. *Neuropsychology*, *9*, 80–90.

Dornonville de la Cour, F., Forchhammer, B., Mogensen, J. & Norup, A. (2018). On the relation between dimensions of fatigue and depression in adolescents and young adults with acquired brain injury. *Neuropsychological Rehabilitation*, *5*, 1–16.

Einarsen, C. E., van der Naalt, J., Jacobs, B., Follestad, T., Moen, K. G., Vik, A. *et al.* (2018). Moderate traumatic brain injury: Clinical characteristics and a prognostic model of 12-month outcome. *World Neurosurgery*, *114*, e1199–e1210.

Forslund, M. V., Perrin, P. B., Røe, C., Sigurdardottir, S., Hellstrøm, T., Berntsen, S. A. *et al.* (2019). Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00219

Garske, G. G. & Thomas, K. R. (1992). Self-reported self-esteem and depression: Indexes of psychological adjustment following severe traumatic brain injury. *Rehabilitation Counseling Bulletin*, *36*, 44–52.

Gorgoraptis, N., Zaw-Linn, J., Feeney, C., Tenorio-Jimenez, C., Niemi, M., Malik, A. *et al.* (2019). Cognitive impairment and health-related quality of life following traumatic brain injury. *NeuroRehabilitation*, *44*, 321–331.

Griffen, J. & Hanks, R. (2014). Cognitive and behavioral outcomes from traumatic brain injury. In M. Sherer & A. M. Sander (Eds.), *Handbook on the neuropyschology of traumatic brain injury, Clinical handbooks in neuropsychology* (pp. 25–45). New York: Springer-Verlag.

Hart, T., Brenner, L., Clark, A. N., Bogner, J. A., Novack, T. A., Chervoneva, I. *et al.* (2011). Major and minor depression after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *92*, 1211–1219.

Hudak, A. M., Caesar, R. R., Frol, A. B., Krueger, K., Harper, C. R., Temkin, N. R. *et al.* (2005). Functional outcome scales in traumatic brain injury: A comparison of the Glasgow Outcome Scale (extended) and the functional status examination. *Journal of Neurotrauma*, *22*, 1319–1326.

Jørgensen, K. (2012). *Danske normer til neuropsykologiske tests* [Danish norms to neuropsychological tests]. Copenhagen: Dansk Psykologisk Forlag.

Kashluba, S., Hanks, R. A., Casey, J. E. & Millis, S. R. (2008). Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *89*, 904–911.

Kersel, D., Marsh, N., Havill, J. & Sleigh, J. (2001). Neuropsychological functioning during the year following severe traumatic brain injury. *Brain Injury*, *15*, 283–296.

Marsh, N. (2019). Cognitive functioning following traumatic brain injury: The first 5 years. *NeuroRehabilitation*, *43*, 377–386.

Meeus, W. (2016). Adolescent psychosocial development: A review of longitudinal models and research. *Developmental Psychology*, *52*, 1969–1993.

Nørgaard, M. & Johnsen, S. P. (2016). How can the research potential of the clinical quality databases be maximized? The Danish experience. *Journal of Internal Medicine*, *279*, 132–140.

O'Connor, S. S., Zatzick, D. F., Wang, J., Temkin, N., Koepsell, T. D., Jaffe, K. M. *et al.* (2012). Association between posttraumatic stress, depression, and functional impairments in adolescents 24 months after traumatic brain injury. *Journal of Traumatic Stress*, *25*, 264–271.

Olsen, L., Jensen, D., Noerholm, V., Martiny, K. & Bech, P. (2003). The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychological Medicine*, *33*, 351–356.

Osborn, A. J., Mathias, J. L. & Fairweather-Schmidt, A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews*, *47*, 1–15.

Poggi, G., Liscio, M., Adduci, A., Galbiati, S., Sommovigo, M., Degrate, A. *et al.* (2003). Neuropsychiatric sequelae in TBI: A comparison across different age groups. *Brain Injury*, *17*, 835–846.

Ponsford, J. L., Downing, M. G., Olver, J., Ponsford, M., Acher, R., Carty, M. *et al.* (2014). Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *Journal of Neurotrauma*, *31*, 64–77.

Reitan, R. (1992). *Trail Making Test. Manual for administration and scoring*. South Tucson, AZ: Reitan Neuropsychology Laboratory.

Ryttersgaard, T. O., Johnsen, S. P., Riis, J. Ø., Mogensen, P. H. & Bjarkam, C. R. (2020). Prevalence of depression after moderate to severe traumatic brain injury among adolescents and young adults: A systematic review. *Scandinavian Journal of Psychology*, *61*, 297–306.

Satz, P., Forney, D. L., Zaucha, K., Asarnow, R. R., Light, R., McCleary, C. *et al.* (1998). Depression, cognition, and functional correlates of recovery outcome after traumatic brain injury. *Brain Injury*, *12*, 537–553.

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F. & Polinder, S. (2016). Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: A systematic review. *Journal of Neurotrauma*, *33*, 1969–1994.

Seel, R. T., MacCiocchi, S. & Kreutzer, J. S. (2010). Clinical considerations for the diagnosis of major depression after moderate to severe tBI. *Journal of Head Trauma Rehabilitation*, *25* 99–112.

StataCorp. (2017). *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.

Statistics Denmark (2015). *Educational attainment (15-69 years) HFUDD10*. Copenhagen: Statistics Denmark.

Stenberg, M., Godbolt, A. K., Nygren De Boussard, C., Levi, R. & Stålnacke, B. M. (2015). Cognitive impairment after severe traumatic brain injury, clinical course and impact on outcome: A Swedish-Icelandic study. *Behavioural Neurology*, *2015*, 680308. https://doi.org/10.1155/2015/680308

Strauss, E., Sherman, E. & Spreen, O. (2006). *A compendium of neuropsychological tests. Administration, norms and commentary* (3rd ed.). New York: Oxford University Press.

Sørensen, H. T., Pedersen, L., Jørgensen, J. & Ehrenstein, V. (2016). Danish clinical quality databases – an important and untapped resource for clinical research. *Clinical Epidemiology*, *8*, 425–427.

Svendsen, S. W. & Ingeman, A. (2017). *Dansk Register for Unge med Erhvervet hjerneskade - DRUE. Baggrund og dataoversigt* [Danish register for young adults with acquired brain injury]. Copenhagen: The Danish Clinical Quality Program - National Clinical Registries.

Tyerman, A. & Humphrey, M. (1984). Changes in self-concept following severe head injury. *International Journal of Rehabilitation Research*, *7*, 11–23.

van Reekum, R., Bolago, I., Finlayson, M. A. J., Garner, S. & Links, P. S. (1996). Psychiatric disorders after traumatic brain injury. *Brain Injury*, *10*, 319–328.

Wechsler, D. (2011). *Wechsler Adult Intelligance Scale - Fourth Edition, WAIS-IV Danish Version*. Stockholm: Pearson Assessment.
Willmott, C., Spitz, G. & Ponsford, J. L. (2015). Predictors of productivity outcomes for secondary and tertiary students following traumatic brain injury. *Brain Injury*, *29*, 929–936.
Wilson, J. T. L., Pettigrew, L. E. L. & Teasdale, G. M. (1998). Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for their use. *Journal of Neurotrauma*, *15*, 573–585.
World Health Organization (2016). *ICD- 10: International statistical classification of diseases and related health problems*. Geneva: World Health Organization.
World Health Organization (2017). Depression and other common mental disorders: Global health estimates. Retrieved 30 August 2019 from https://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/

Received 27 January 2020, accepted 11 May 2020

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Supplementary Material 1: Major (ICD-10) Depression Inventory.
Supplementary Material 2: Educational attainment (15-29 years).
Supplementary Material 3: Distribution of depression and cognitive sequelae.

Appendix D. Paper III

Depression and cognitive sequelae after a traumatic brain lesion

Ryttersgaard TO[a,d], Riis JØ[b], Johnsen SP[c], Mogensen PH[a], Bjarkam CR[b,d].

Paper accepted for publication in Danish Medical Journal, 2022.

The paper has been made available for the assessment committee

Affiliations:
a) Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
b) Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark
c) Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark
d) Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Appendix E. Paper IV

Use of antidepressants among adolescents and young adults with traumatic brain injury

Ryttersgaard TO[a,d], Valentin JB[b], Johnsen SP[b], Riis JØ[c], Bjarkam CR[c,d]

Paper submitted 2022.

The paper has been made available for the assessment committee

Affiliations:

a) Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
b) Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark
c) Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark
d) Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-912-7

AALBORG UNIVERSITY PRESS