Long-term Outcome in Children and Youth with Acquired Brain Injury

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Chapter 1

General introduction

ACQUIRED BRAIN INJURY IN CHILDREN AND YOUTH

Acquired brain injury (ABI) refers to any damage to the brain that occurs after the neonatal period, rather than as part of a genetic or congenital disorder [1]. It is a leading cause of morbidity and mortality in children and adolescents in first-world nations [2, 3]. Brain injury due to trauma (traumatic brain injury, TBI) is the most common cause of ABI. Other causes (non-traumatic brain injury, nTBI) are for example brain tumor, stroke or infection of the brain. This thesis is on ABI in children and youth. In children aged 0–4 years accidents at home are the most common cause of TBI and infections of the brain (meningitis) for nTBI. In children and youth aged 5–24 years traffic accidents are by far the most common cause for TBI and hypoxic-ischemic events and brain tumors for children were mostly seen between 5–14 years [4].

Severity of ABI is classified as mild, moderate or severe. TBI is categorized based on the Glasgow Coma Scale (GCS) score at time of presentation in the emergency room in mild (GCS 13–15), moderate (GCS 9–12) and severe (GCS 3–8) TBI. Other measures for determination of the severity in TBI are the duration of the posttraumatic amnesia and the loss of consciousness [5]. Severity of nTBI can be classified using the modified paediatric Ranking Scale (mRS), assessed at discharge from the hospital (mild mRS 0–1, moderate mRS 2–3, severe mRS 4–5) [6].

In the Netherlands, the estimated yearly incidence rates for children and youth until 24 years, are 585 per 100,000 for TBI and 190 per 100,000 for nTBI, of which 15–20% is classified as moderate or severe. On average, in the Netherlands 15,000 children and youth (0–24 years) are diagnosed with TBI every year and 5,000 are diagnosed with nTBI (0–24 years) with varying severity of long-term sequalae in daily life [4, 7]. It is to be noted that these are hospital based numbers. Especially children and youth with mild TBI are not always referred to a hospital. The actual number therefore may be higher.

In children, neuropathology caused by brain injury is assumed to have more serious and persisting consequences than in adults due to the immaturity of the young brain and the risk to disrupt ongoing brain development and brain maturation [8, 9]. The damage to the brain can be focal or multifocal dependent on the variety of mechanisms of injury and structures and networks affected. Therefore ABI is a complex phenomenon.

Functional outcome, participation, quality of life and family impact

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) of the World Health Organization (WHO) is widely used in clinical practice and

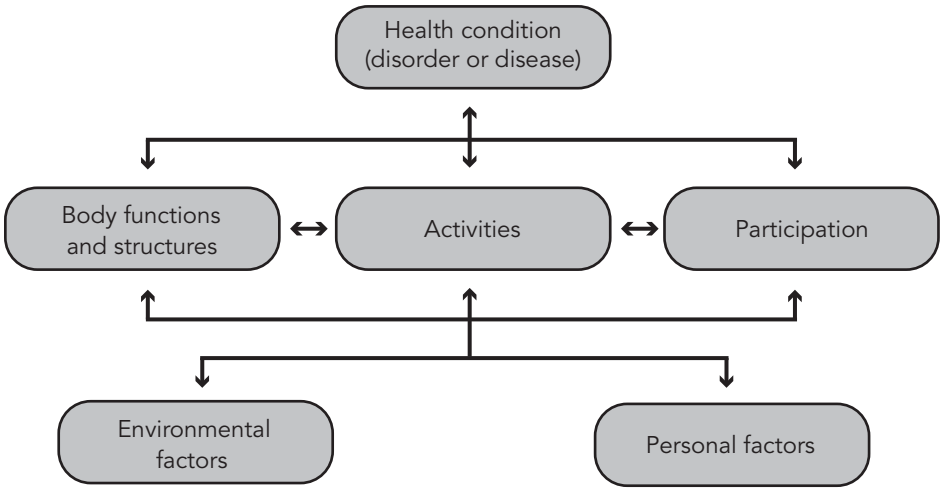

Figure 1.1 The International Classification of Functioning, Disability and Health (ICF model).

outcome research as a structuring framework to describe and understand the complex interaction between the health problem (ABI) and its consequences [10, 11] (see Figure 1.1). This framework represents a broad view of functioning across all health-related domains like body function and structures, activities and participation accounting for environmental and personal factors. Body functions and structures are defined as physiological functions and anatomic characteristics of body systems, like physical and mental functions. Activities are defined as the execution of tasks or actions by a person, like mobility and self-care. Participation is defined as a person's involvement in meaningful life situations in several settings like home, school and community life. Personal factors (e.g. age, sex, ethnicity) and environmental factors (e.g. family situation and socio-economic status) can influence these functions, activities and participation [12].

The WHO defines quality of life as the individuals' perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns [13]. Health related quality of life (HRQoL) refers to the impact of health and illness on an individual's quality of life [14] and is reported as important health problem of ABI [15–18].

ABI in children and youth may cause a variety of long-term disorders in body functions (deficits) across motor, language, cognitive and behavioral domains which may have a negative impact on activities, participation and health-related quality of life [19–23]. In children and youth with TBI, persistent cognitive and behavioral impairments are reported

[24, 25]. In children with moderate and severe ABI cognitive and behavioral function may deteriorate when environmental demands on the child increase further impeding participation and affecting quality of life [24, 26–29].

On the long-term, defined as six months or longer post-injury, 30–70% of the children and youth with ABI are restricted in at least one domain of participation, depending on the studied population [19, 22, 28, 30]. In children with ABI, HRQoL may be low both for the affected child and for the caregivers [31–34]. Changes in the life course development of the children and their families are reported, leading to stress in approximately 40% of families more than 12 months after onset [35, 36]. Children and youth with moderate or severe ABI are reported to have substantial long-term participation problems and reduced HRQoL compared to their peers [31, 37]. In contrast, in the majority of children and youth with mild TBI postconcussion symptoms and cognitive and behavioral deficits resolve over time [38]. However, 10–20% of them experience a complicated recovery with lowered satisfaction with life and impaired cognitive functions on the long-term [24, 39–42].

Although the potential negative impact of ABI is documented, little is known about what predictors relate to an unfavorable outcome. Insight in predictors of unfavorable outcome is of pivotal importance in planning integrated care pathways. This thesis therefore focuses both on long term outcome after ABI and on the determinants of outcome. Besides investigation of a heterogeneous sample of children with ABI comprising both those with TBI and nTBI also subsamples of TBI and mild TBI are investigated to get more insight in the outcome of the different groups.

Determinants of outcome

Multiple factors seem to be related to neurological outcome, participation and quality of life in children and youth with ABI [25, 43, 44]. These factors can be divided into child-specific factors, injury-related factors and socio-environmental factors. Child-specific factors are a combination of personal factors (such as age), health-related factors (such as pre-injury comorbidities) and body functions (such as cognition) [19]. Injury-related factors involve primary and secondary brain injury mechanisms as well as other injuries of the body. Socio-environmental factors are aspects of the physical, social and environment in which people live their everyday lives. Predictors of outcome may support clinical decision making in planning care pathways. Identification of modifiable predictors provides the opportunity to intervene and potentially modify outcome.

The ICF-CY model illustrates that outcome after ABI covers multiple domains. Previous research has focused on neurological (motor and cognitive) outcome and its determinants

[20, 23, 28, 45]. Only recently predictors of psychosocial outcome, participation and quality of life are being studied too. A systematic review on five included studies until 2012, focused on long-term participation after ABI in children and youth [44]. Two reviews investigated long-term psychosocial outcome (behavioral and adaptive functioning) after TBI in children [25, 46]. No systematic reviews have been published so far on prognostic factors for long-term participation after TBI in children and only two on long-term HRQoL after TBI in children [31, 47].

So far, long-term consequences of childhood ABI, defined as six months or longer post-injury, have received limited attention and remain poorly understood particularly for children with mild brain injury. More knowledge is needed about predictors of functional outcome. Clinical perceptions of long-term outcome may be negatively skewed, since only those children with severe and persisting problems are presenting for healthcare services on the long term. Prediction of long-term functioning, participation and HRQoL after brain injury in children and youth may help early identification and effective monitoring of vulnerable children. Besides that, it helps to provide education to family or caregivers, to target interventions and to optimize the use of scarce resources in long-term treatment planning. Early prediction of outcome in children with ABI is critical in relation to the development of brain functions and to start interventions at the right time for the affected child to achieve optimal recovery of functioning, to continue learning and to adapt to social roles.

AIM OF THIS THESIS

The primary aim of this thesis is to describe the long-term neurological outcome and participation of children and youth with ABI, the HRQoL of children and caregivers and to investigate associated factors and inter-relationships. A systematic review about long-term participation and HRQoL in children and youth with TBI was performed and a cross-sectional study was performed at two years after ABI in children and youth (aged 6–22 years) living in the south-west region of the Netherlands.

OUTLINE OF THIS THESIS

In chapters 2 to 5 we will report on long-term outcomes and associated factors of children and youth after ABI, including both TBI and nTBI. In these chapters we will address different outcomes, i.e. neurological outcome, participation, HRQoL and family impact. **Chapter 2** describes a systematic review of the literature about long-term participation

and HRQoL in children and adolescents diagnosed with TBI to gain a more precise overview of all factors related to participation and HRQoL on the long-term (≥6 months post TBI) at school age between 4 and 18 years old. Potential predictors were divided in child-specific factors (demographic factors and child functioning factors), injury-related factors and socio-environmental factors. **Chapter 3** describes neurological outcome two years after brain injury and its correlations with sociodemographic, injury-related, child-function (pre-injury developmental status and current education level) and family related characteristics. In addition, associations of neurological outcome with activity limitations and participation restrictions were explored. **Chapter 4** describes the HRQoL of children and youth with acquired brain injury, two years post-injury, compared with age-appropriate reference values of the Dutch population and describes associations of their HRQoL with sociodemographic, injury-related, child-function (pre-injury developmental status and post-injury problems, severity of impairments and level of education) and family-related characteristics. **Chapter 5** describes the parent-reported impact of ABI, two years after diagnosis. An important intent was to investigate whether previous findings from US studies generalize to the Netherlands and whether these differ between children with TBI or nTBI. Secondary aim was to determine associations between family impact and sociodemographic, injury-related, child-function (actual) and family-related characteristics. **Chapter 6** describes cognitive functioning of children and adolescents two years after sustaining mild TBI and its correlations with sociodemographic, injury-related and child-function (pre-injury developmental status, education level and post-injury problems) characteristics. In addition, associations between cognitive outcome and level of participation were explored. **Chapter 7** describes the study protocol of the Brains Ahead! Study. During the interpretation of the results of the earlier mentioned cross-sectional study this multicenter study is invented. Participation and activity levels of children and adolescents during the first six months after mild TBI are monitored and we aim to identify outcome predictors. The second aim of this study is to investigate the effect of an early psychoeducational intervention on functional outcome, participation and HRQoL. **Chapter 8** presents the general discussion of the main findings, future research perspectives and general conclusion with clinical implications.

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Chapter 2

Predictors of long-term participation and health-related quality of life in school-aged children and adolescents with traumatic brain injury: systematic review

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Abstract

Introduction: Consequences of traumatic brain injury (TBI) may include limitations of daily activities and restrictions in participation. Limitations in activities are assumed to have considerable impact on children's participation and quality of life (QoL). The aim of this systematic review is to identify which factors are associated with participation and quality of life in children with TBI.

Methods: A systematic search in Pubmed, Embase and Web of science was performed until the 14th of May 2018. Studies describing determinants of participation and quality of life at least 6 months after the diagnosis of TBI by means of one or more pre-defined instruments in patients up to 18 years of age were included. Extracted data included study characteristics, patient characteristics, participation and QoL outcome measures and determinants.

Results: The search strategy yielded initially 3,132 records. After exclusion of all the duplicates the search yielded 2,256 unique records. Subsequently, from the title and abstract screening 2,182 records were excluded from the study because they did not fit the inclusion criteria. For the full text screening 74 articles were retrieved and evaluated. From this step 32 articles remained.

Conclusion: Significant associations were found between the related factors of the categories, child-specific, injury-related and socio-environmental, and long-term participation and QoL in children with TBI. Most evidence was found for post-injury cognitive function problems in relation to more restrictions in more than one dimension of participation.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of mortality and of disability among children and adolescents [1]. TBI may cause focal or multifocal alterations in brain function [2], affecting motor, communication, cognitive and behavioural functions impairing health-related quality of life (HRQoL) and participation at home, school and in the community, even on the long-term [3–9]. The effects of TBI in children may be more severe and persisting than in adults due to the immaturity of the young brain and the risk to disrupt ongoing brain development [10, 11].

Prediction models for long-term outcome are essential to optimize health care and follow-up, especially on participation and HRQoL. To our knowledge no systematic reviews have been published on prognostic factors for long-term participation after TBI in children and only two on HRQoL [8, 12]. Di Battista et al. used various definitions of quality of life (QoL) and the searches were limited to studies published before 2010 [8]. They found that the difference between good and poor QoL was due to severity of injury, timing of outcome assessment and definition of QoL. Fineblit et al. focused on mild TBI (mTBI). They found that potential predictors of poor HRQoL after mTBI include older age, lower socioeconomic status, or a pre-injury history of headaches or sleeping disorder [12]. There is one systematic review concerning associated factors for long-term participation after acquired brain injury (ABI) in children and youth and several factors were found to be associated with participation [3]. Two other reviews investigated long-term psychosocial outcome (behavioural and adaptive functioning) after TBI in children [13–14]. Injury severity and several pre-injury psychosocial factors were identified as significant predictors of psychosocial outcome and appear to be moderated by the family environment.

TBI in children may have serious and even lifelong consequences affecting participation and HRQoL. Prediction of long-term outcome after TBI in children and adolescents may help to identify and closely monitor vulnerable patients, and to optimize the use of scarce resources in long-term treatment planning. The aim of this review is therefore to systematically review the literature for all factors related to long-term (≥6 months post TBI) participation and HRQoL after TBI at school age between 4 and 18 years old. Firstly, the most frequently used instruments will be selected to measure participation and HRQoL. Secondly, potential predictors are divided in 1) child-specific factors, divided in demographic factors and child functioning factors, 2) injury-related factors, such as severity of injury and complications and 3) socio-environmental factors, such as family environment and social economic status. We hypothesized that child-specific factors such as higher age at injury and better functioning of the child are associated with better participation

and HRQoL at least 6 months post-injury. Likewise, we hypothesized that less severe injury is associated with better participation and HRQoL at least 6 months post-injury. Finally, we hypothesized that better socio-environmental factors are associated with better participation and HRQoL at least 6 months post-injury.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) [15].

Search strategy

The used search terms incorporated the terms as 'traumatic brain injury', 'participation', 'activity' and 'quality of life' (see Appendix 2.1). The search was restricted to children and adolescents with a mean age between 4 to 18 years old. The databases used for this search strategy were Pubmed, Embase and Web of Science. The search was performed on the 14th of May 2018 by S.L.

Data collection and analysis

Inclusion criteria

The articles had to include participants with TBI defined as: a history of observed loss of consciousness after a head trauma, and/or symptoms related to brain injury, and/or the presence of post-traumatic amnesia, and/or abnormalities at neurological examination, and/or acute traumatic abnormalities on scan images of the brain. The mean age of the participants in the studies had to be between 4 and 18 years old. Only studies investigating participants at least six months after injury were included. Outcome should be described using an explicit outcome measure of participation or HRQoL. We defined participation as involvement in life situations in different domains, i.e.: education, social participation and communication, return to play, community integration, self-care, domestic life, sports participation, interpersonal interactions and relations, according to the International Classification of Functioning, disability and health-Children and Youth (ICF-CY) [16]. QoL is defined as the multiple domains involving subjective wellbeing, similarity between expectation and actual functioning and having the resources to participate [8, 17–19]. Consequently, the article should include measurement instruments assessing at least two domains of participation or HRQoL respectively. Measurement instruments were administered as self-report or parent-report questionnaires.

Exclusion criteria

All articles about non-traumatic brain injury were excluded, except if they also analysed a TBI category separately. Likewise minor head injuries, which did not fit into the definition of TBI, were excluded. Papers in other languages than English, Dutch or German were excluded. Also, single- case reports were excluded.

Article selection procedure

Title and abstract screening

Two independent reviewers- L.J. and S.L. were involved in the selection of the articles. If there was no consensus between the reviewers, the article was again revised by both reviewers and if needed a decision was made by a third person (I.P.). In the first stage the articles were selected based on titles and abstracts. All irrelevant titles and abstracts were excluded as well as double hits of an article throughout the different databases.

Selection of full text articles

Subsequently, out of the remaining titles and abstracts full text versions were selected or requested from the authors if not available. If multiple articles were found reporting the same relationships in the same cohort, the most recent article was chosen. If multiple articles were found reporting different associations in the same cohort, all were included. The measurement instrument that was most frequently used in the articles was selected as primary outcomes for respectively participation and HRQoL. All other instruments were categorized as secondary outcomes, which were not further analysed.

Primary outcome measures

The most frequently used outcome measures for the assessment of participation and HRQoL are the Child and Adolescent Scale of Participation (CASP) [20] and the Pediatric Quality of Life (PedsQL) [21] respectively. The CASP questionnaire is suitable for use and recommended for children and adolescents with TBI [22]. It defines participation as home participation, school participation, community participation and home and community activities. The items are scored according to a 4-point Likert Scale and the summary for each item could be transformed in a 100-point scale. Higher scores indicate a better participation outcome. The CASP has a Cronbach's alpha of .98 and a test-retest reliability of .94.

The PedsQL questionnaire is suitable for use and recommended for children and adolescents with TBI [22]. It consists of a 15-item measure of global HRQoL and in addition

it contains eight supplemental modules, which assesses the specific symptoms or treatment domains: physical functioning, psychosocial functioning and social functioning. The items are scored according a 4-point scale and the total score can be converted in a 100-point scale. Higher scores indicate a higher HRQoL. The Cronbach's alpha is .83 for the child and .86 for the caregiver [21, 23].

Data extraction

The following data were extracted; title of the article, author(s), country of the study, year of publication, type of study design (cross- sectional, longitudinal etc.), duration of the follow- up, time since injury, injury severity (mild, moderate or severe), population, outcome measures of participation and HRQoL and corresponding outcome measurements expressed in a statistic value. Furthermore, the independent variables predicting either participation or HRQoL were grouped according to the following categories: 1) child-specific- (demographic and functioning), 2) injury-related-, and 3) socio-environmental factors.

Methodological quality

The methodological quality and the risk of bias of every article was assessed with a quality assessment tool for systematic reviews obtained from Cochrane Libraries, Quality in Prognostic Studies (QUIPS) [24] by L.J. and S.L. In case of disagreement a decision was made by a third person (I.P.). This tool consists of 41 items in six domains; study participation (6 items), study attrition (5 items), prognostic factor measurement (6 items), outcome measurement (3 items), study confounding (7 items) and statistical analysis and reporting (4 items). Bias in each domain is rated as high, moderate or low risk of bias and low risk in this case means high methodological quality of the study. The studies were defined as low risk of bias if the score on all six domains was low.

Data synthesis

The associated factors are described according to time since injury and for each variable four levels of evidence were possible (criteria adapted from De Croon et al.) [25, 26]. See Table 2.1. An association was classified as positive if people with a higher score on the variable of interest were more likely to participate or had a better HRQoL. An association was classified as negative if people with a lower score on the variable of interest were more likely to participate or had a better HRQoL. Studies of the same cohort were taken together and were counted as one study.

Table 2.1 Four levels of evidence for associated factors

Level of evidence	
Strong evidence	• Three studies available from different cohorts that found a significant association in the same direction • More than four studies available from different cohorts of which ≥75% found a significant association in the same direction and ≤25% found an opposite association
Weak evidence	• Two studies available from different cohorts that find a significant association in the same direction • Two studies available from different cohorts that found no association • Three studies available from different cohorts of which two found a significant association in the same direction and the third study found no significant association
No evidence	• ≤ one study or cohort available
Inconsistent	• All remaining cases

RESULTS

Identification

The search strategy yielded initially 3,132 records from which 576 records were duplicates. After exclusion of all the duplicates the search yielded 2,256 unique records. Based on title and abstract screening 2,182 records were excluded from the study because they did not fit the inclusion criteria. For the full text screening 74 articles were retrieved and evaluated. From this step 32 articles remained (Figure 2.1). Main reasons for exclusion were age at injury, not describing potential predictors for participation and/or HRQoL, qualitative research, conference abstracts or single-case reports. Nineteen articles used the most common outcome measure for participation and HRQoL, the Child and Adolescent Scale of Participation (CASP) [20] and the Pediatric Quality of Life (PedsQL) [21] and were analyzed. Studies using other scales than the CASP or PedsQL were excluded [27–39].

Study characteristics

Nineteen articles met the outlined inclusion criteria, eight articles studying potentially related factors to participation (CASP) [40–47] and 11 articles studying HRQoL (PedsQL) [48–58]. Tables 2.2 (Participation) and 2.3 (HRQoL) summarize the key methodological characteristics of each of these studies, including authors, design, sample characteristics, included variables and findings.

Table 2.2 Characteristics of studies of participation measured with CASP in children and adolescents with TBI

Author(s), country and design	Year	N	Age (y)	Male %	% severity	Variables (measures)	Time since injury (mean)	Outcome CASP total score
Australia Melbourne Prospective cohort								
1. Anderson et al. [40]	2013	N=93 TBI N= 43 TD	5–15	69.8	64.5% mild 35.5% mod/sev	Age, gender, language competence (TLC-E)* at 6 m, verbal IQ (WASI) at 6 m, PSI* at 6 m, severity* (GCS), site of pathology (MRI-scan), SES, pre-family functioning* (FAD)	6 m	98.7 mild 94.3 mod/sev
2. Catroppa et al. [41]	2015	N=97 TBI N=43 TD	5–15	69.1	63.9% mild 21.6% mod 14.4% sev	Severity (GCS)*, pre-social and behaviour* (ABAS, CASP, CBCL), family functioning (SES, FAD, GHQ), Restrictions of participation (as rated by clinicians)	6 m	98.4 mild 95.5 mod 89.1 sev
3. Catroppa et al. [42]	2017	N=79 TBI N=35 TD	5–16	68.4	64.6% mild 24.1% mod 11.4% sev	Severity (GCS), site of pathology (MR-scan), pre-social and behaviour (ABAS,CASP,CBCL)*, SES (AUSEI06) family functioning (FAD, GHQ), self-esteem (HSPPC)	1 y	98.3 mild 95.8 mod 98.2 sev
4. Anderson et al. [43]	2017	N=74 TBI N=39 TD	5–16	64.9	51.4% mild 48.6% mod/sev	Age, gender, severity (GCS), location and volume of lesions (SWI MRI-scan), family functioning (FAD, GHQ) pre-injury and at 2 y, family burden (FBII) at 2 y, SES (AUSEI06) at 2 y, IQ at 6 m (WASI), child behaviour: internalizing* and externalizing (CBCL) at 2 y, communication (TLC-E) at 2 y, PSI at 2 y	2 y	98.97 mild 98.63 mod/sev
The Netherlands Cross-sectioneel								
5. Lambregts et al. [44]	2018	N=73	4–20	56.2	100% mild	Processing speed, inhibitory control (speed* and accuracy), cognitive flexibility (speed and accuracy), visuomotor coordination, visuospatial constructional ability, visuspatial memory*, verbal working memory*	2 y	94.09 total

Table 2.2 *Continued*

Author(s), country and design	Year	N	Age (y)	Male %	% severity	Variables (measures)	Time since injury (mean)	Outcome CASP total score
Canada Quebec Cross-sectioneel								
6. Sirois et al. [45]	2017	N=23 TBI N=23 TD	12–21	60.9	0% mild 100% mod/sev	mentalising*, social knowledge, facial emotion recognition (subtests BICS); selective and sustained attention (D2 attention test), verbal working memory (Digit Span task), planning and problem solving* (D-KEFS)	2 y	87.98 mod/sev[a]
USA Ohio Cross-sectioneel								
7. Schultz et al. [46]	2016	N=69 TBI N=60 OI	8–13	66.7	72.5% mild/mod 27.5% sev	Severity (GCS)*, Post executive function (TEA-Ch), post PSI in severe injury * (subtest WISC-IV)	12–63 m (2.7 y)	96.87 mild/mod 93.64 sev
Canada Ontario Cross-sectioneel								
8. Wells et al. [47]	2009	N=30	0–10	60.0	56.7% mild 10.0% mod 33.4% sev	Age*, time since injury, severity* (GCSR, STSR, CTSR*), parent education, household income, number of parents in home, environment* (CASE)	4–16 y (10 y)	88.89 total

CASP, Child and Adolescent Scale of Participation; TBI, Traumatic Brain Injury; TD, Typical Developing children; mod, moderate; sev, severe; y, year; m, month; GCS, Glasgow Come Scale; SES, Socioeconomic status; FAD, Family Assessment Device; WASI, Wechsler Abbreviated Intelligence Scale; TLC-E, Test of Language Competence-Expanded Edition; PSI, Processing Speed Index; ABAS II, Adaptive Behaviour Assessment Scale; CBCL, Child Behaviour Checklist; GHQ, General Health Questionnaire; AUSEI06, Australian Socioeconomic Index 2006; HSPPC, Harter Self Perception Profile for Children; SWI, susceptibility weighted imaging; FBII, Family Burden of Injury Inventory; OI, Orthopedic Injury; BICS, Batterie Integree de Cognition Sociale; D-KEFS, Delis–Kaplan Executive Function System; TEA-Ch, Test of Everyday Attention for Children; WISC-IV, Wechsler Intelligence Scales for Children-fourth edition; GCSR, Glasgow Coma Scale Severity Ratings; STSR, Standardized Test Severity Rating; CTSR, Clinical Team Severity Ratings; CASE, Child and Adolescent Scale of Environment.
* Significant related factor.
a CASP, completed by youth themselves.

Table 2.3 Characteristics of studies of Health-Related Quality of Life measured with PedsQL in children and adolescents with TBI

Author(s), country and design	Year	N	Age (y)	Male %	% severity	Variables (measures)*	Time since injury	PedsQL score
USA Washington Prospective cohort								
1. Rivara et al. [48]	2011	N=729 TBI N=197 AI	0–17	68%	84.5% mild 13.2% mod 2.3% sev	Age, gender, severity* (GCS and CT-scan), household income*, respondent education, lowest motor GCS, family functioning (FAD) at baseline, PedsQL at baseline*	(3), 12, 24 m	*12 m:* 81.7–82.7 mild 75.6 mod 66.4 sev *24 m:* 82.0–85.2 mild 76.2 mod 68.1 sev
2. Swanson et al. [49]	2012	N=347	2–17	71.2%	57.9% normal CT 42.1% abnormal CT	Intracranial injuries (CT-scan)* (especially midline shift ≥5 mm), baseline PedsQL, age, gender and non-head Maximum Abbreviated Injury Scoring (MaxAIS)	12 m	-
3. O'Conner et al. ** [50]	2012	N=189 TBI N=39 AI	14–17	71.4%	83.6% mild 16.4% mod/sev	Severity (GCS and CT-scan), Post depression (PHQ-9)*, PTSD (UCLA PTSD Reaction Index)*, baseline family functioning (FAD), mechanism of injury, pre-injury depression (PHQ-9), pre-injury mental health, family income level, parents highest level of education, parental marital status, admission to IC, history of learning disabilities, pre-injury QoL	(3), 12, 24 m	-
4. Rivara et al. [51]	2012	N=595 TBI N=174 AI	0–17	69.9%	86.2% mild 11.6% mod 2.2% sev	Age, gender, severity* (GCS and CT-scan), ethnicity, household income, respondent education, lowest motor GCS, family functioning (FAD) at baseline, PedsQL at baseline	24, 36 m	*36 m:* 82.0–86.3 mild 71.3 mod 67.2 sev

Table 2.3 *Continued*

Author(s), country and design	Year	N	Age (y)	Male %	% severity	Variables (measures)*	Time since injury	PedsQL score
5. Jimenez et al. [52]	2013	N=74 (Hispanic) N=457 (NHW)	0–17	65.3%	75.7% mild Hispanic 20.3% mod Hispanic 4.1% sev Hispanic 88.9% mild NHW 10.3% mod NHW 0.9% sev NHW	Ethniciteit*, family functioning (FAD), age, gender, severity (GCS and CT-scan) and intention of injury, health insurance, household income, respondent education	(3), 12, 24, 36 m	-
6. Zonfrillo et al. [53]	2014	N=311	0–17	64.0%	100% mild	Age, gender, ethnicity, respondent education*, household income*, health insurance*, family functioning (FAD), pre-injury comorbidities, headache scale*, sleepproblems* (subcomponent of the PedsQL), depressive symptoms (PHQ-9), PTSD (UCLA PTSD Reaction Index)	(3), 12 m	-
Europe UK Prospective cohort								
7. Calvert et al. [55]	2008	N=81	5–16	64.2%	45.7% mild 18.5% mod 35.8% sev	King's Outcome Scale for Childhood Head Injury (KOSCHI), severity (GCS, length of PTA)	(1), 6 m	-
USA 4 states Prospective cohort								
8. McCarthy et al. [56]	2006	N=330	5–15	69.4%	56.1% mild 31.2% mod 12.7% sev	Severity (AIS)*, lower extremity fracture, upper extremity fracture*, spinal injury, mechanism of injury, pre-psychosocial conditions*, pre-physical conditions, family functioning (FAD)*, health insurance*, single-parent households*	(3), 12 m	80.0 mild 76.4 mod 70.3 sev

Table 2.3 continues on next page.

Table 2.3 *Continued*

Author(s), country and design	Year	N	Age (y)	Male %	% severity	Variables (measures)*	Time since injury	PedsQL score
Australia Melbourne Cross-sectional								
9. Green et al. [54]	2013	N=17 TBI parents N=16 TD	15–18	58.8%	11.8% mild 52.9% mod 35.3% sev	Post psychosocial reintegration* (SPRS-C), severity* (GCS and CT-scan)	13–16 y	-
Europe UK Cross-sectional								
10. Limond et al. [63]	2009	N=47	5–16	-	72% mild 16% mod 12% sev	Severity (GCS), healthcare services, Scottish Index of Multiple Deprivation (SIMD)	12–60 m (mean 34 m)	-
Australia Cross-sectional								
11. Di Battista et al. [64]	2014	N=11	11–16	63.6%	36.4% mild 63.6 mod/sev	Age at injury* (n.s in regression model), depression (CDI or CESD)*, anxiety (SCARED or STAI), Loneliness (PNDLS), IQ (WASI), severity (Mayo Classification System)	1.92–10.75 y (mean 4.6 y)	-

PedsQL, Pediatric Quality of Life; TBI, Traumatic Brain Injury; AI, Arm Injury; TD, Typical Developing children; y, year; m, month; GCS, Glasgow Coma Scale; FAD, Family Assessment Device; PedsQL, Pediatric Quality of Life Inventory; PHQ-9, Patient Health Questionnaire; NHW, Non-Hispanic White; PTSD, Posttraumatic stress disorder; SPRS-C, Sydney Psychosocial Reintegration Scale for Children; AIS, Abbreviated Injury Scale; n.s., non significant; CDI, Child Depression Inventory; CESD, Centre for Epidemiology Studies Depression Scale; SCARED, Screen for Anxiety Related Disorders; STAI, State-Trait Anxiety Inventory; PNDLS, Peer Network and Dyadic Loneliness Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

* Significant predictor.

** PedsQL (social, school and physical subscales) Cognitive subscale was used as outcome for cognitive functioning.

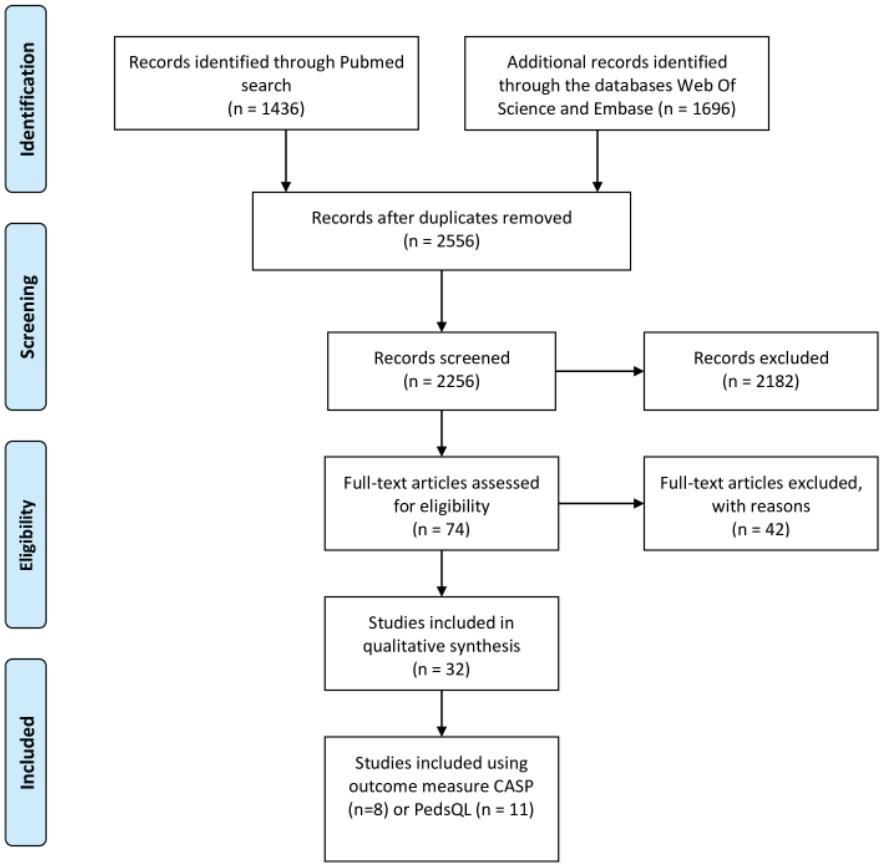

Figure 2.1 Flow diagram showing the selection of the studies.

Of the 19 studies, 12 used prospective and longitudinal designs (63%), and the remaining seven studies used cross-sectional designs (37%). Most studies differentiate the TBI samples into severity groups based on the initial GCS dividing in mild, moderate and severe. Time of assessment varied in most studies between six months and three years after injury.

Four out of eight studies measuring long-term participation were based on the same (Australian) prospective cohort, measuring at different time points and different associated factors [40–43]. The other four studies used a cross-sectional design [44–47]. All studies about participation together contained 292 children and adolescents with TBI. The sample size of the studies varied from 23 to 97. All these studies only present parent-reported answers. The total score of participation (CASP) varied between 87.98 and 98.97.

Six of the 11 studies, measuring long-term HRQoL at different time points and measuring different associated factors, used the same prospective cohort [48–53]. Two other studies used a separate prospective cohort [55, 56] and the other three studies used a cross-sectional design [54, 57, 58]. All studies about HRQoL together contained 1,255 children and adolescents with TBI. The sample size from the studies varied from 11 to 769. One study about 11 participants (0.9%) represent self-reported answers from adolescents, the other studies present parent-reported answers. The total score of HRQoL (PedsQL) varied between 66.4 and 86.3.

Methodological quality of the studies

The methodological quality of the included studies was assessed through the assessment tool QUIPS [24]. Further details are described in Table 2.4. All studies measuring participation were considered to have high methodological quality and therefore low risk of bias. Three out of 11 studies measuring HRQoL were considered to have moderate methodological quality and therefore moderate risk of bias, the remaining eight studies measuring HRQoL were considered to have high quality.

Overview of factors related to participation by category

Significant factors associated with participation more than six months after injury are described in Table 2.5 and the evidence for the prognostic value is described in Table 2.6.

1) Child specific factors

Child demographics: Inconsistent evidence was found for age at injury as predictor of long-term participation. In the prospective Australian cohort [40, 43] no association was found between age at injury and long-term participation and in another cross-sectional study [47] including young children with a mean age of 5.3 years at injury, a younger age at onset predicted less participation at 10 years post-injury.

Child function factors: Strong evidence was found for cognitive functioning post-injury as predictor of long-term participation. Cognitive functioning was based on neuropsychological assessments and studied in five studies [40, 43–46] and the following associations were found cross-sectionally: worse language competence post-injury was associated with reduced participation at six months post-injury [40]; mentalizing problems and planning/problem solving difficulties were related to reduced participation at two year post-injury [45]; slower processing speed was related to reduced participation at six months and three year post-injury [40, 46]. Slower inhibition speed, impaired visuospatial

Table 2.4 Methodological quality (QUIPS) of studies measuring participation and health-related quality of life

Author	1. Study participation	2. Study attrition	3. Prognostic factor measurement	4. Outcome measurement	5. Study confounding	6. Statistical analysis and reporting	Total risk of bias	Methodological quality of study
Participation								
1. Anderson [40]	Low	Low	Low	Low	Low	Low	Low	High
2. Catroppa [41]	Low	Low	Low	Low	Low	Low	Low	High
3. Catroppa [42]	Low	Low	Low	Low	Low	Low	Low	High
4. Anderson [43]	Low	Low	Low	Low	Low	Low	Low	High
5. Lambregts [44]	Low	Low	Low	Low	Low	Low	Low	High
6. Sirois [45]	Low	Low	Low	Low	Low	Low	Low	High
7. Schultz [46]	Low	Low	Low	Low	Low	Low	Low	High
8. Wells [47]	Moderate	Low	Low	Low	Low	Low	Low	High
Health-related quality of life								
1. Rivara [48]	Low	Moderate	Low	Low	Low	Low	Low	High
2. Swanson [49]	Low	Low	Low	Low	Low	Low	Low	High
3. O'Connor [50]	Low	Moderate	Low	Low	Low	Low	Low	High
4. Rivara [51]	Low	Moderate	Low	Low	Low	Low	Low	High
5. Jimenez [52]	Low	Low	Low	Low	Low	Low	Low	High
6. Zonfrillo [53]	Low	Moderate	Low	Low	Low	Low	Low	High
7. Green [54]	Low	Low	Low	Low	Low	Low	Low	High
8. Calvert [55]	Low	Moderate	Low	Low	High	Low	Moderate	Moderate
9. McCarthy [56]	Low	Low	Low	Low	Low	Low	Low	High
10. Limond [57]	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
11. DiBattista [58]	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate

Table 2.5 Predictors or associations of participation measured with CASP in children and adolescents with TBI

Study	6 m	1 y	2 y	≥3 y
Australia Melbourne Prospective Cohort				
1. Anderson 2013 [40]	Severity of injury (GCS) Post language competence at 6 m Processing speed at 6 m Pre-family functioning			
2. Catroppa 2015 [41]	Severity of injury (GCS) Pre-social and behaviour functioning			
3. Catroppa 2017 [42]		Pre-social and behaviour		
4. Anderson 2017 [43]			Post internalising behaviour at 2 y	
The Netherlands Cross-sectional				
5. Lambregts 2018 [44]			Inhibition speed at 2 y Visuospatial memory at 2 y Verbal working memory at 2 y	
Canada Quebec Cross-sectional				
6. Sirois 2017 [45]			Post mentalising at 2 y Post planning/problem solving at 2 y	
USA Ohio Cross-sectional				
7. Schultz 2016 [46]				Severity Post processing speed at 2.7 y in severe injuries
Canada Ontario Cross-sectional				
8. Wells 2009[a] [47]				Age Environment (CASE) Severity within 1 y (CTSR)

CASP, Child and Adolescent Scale of Participation; TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; m, month; y, year; CASE, Child and Adolescent Scale of Environment; CTSR, Clinical Team Severity Ratings; a Time since injury 4–17 y.

Table 2.6 Overview of the evidence for the prognostic value of factors concerning participation

Variable	Positive association	Negative association	No association	Evidence
Child demographics				
Age	47		40*, 43*	Inconsistent
Gender			40*, 43*	No evidence
Child function factors				
Pre-injury social and behaviour problems		41*, 42*		No evidence
Post-injury behaviour problems		43*		No evidence
Post-injury intelligence			40*, 43*	No evidence
Post-injury cognitive function problems		40*, 44, 45, 46	43*	Strong (yes)
Injury-related factors				
Severity		40*, 41*, 46, 47	42*, 43*	Inconsistent
Socio-environmental factors				
Family functioning	40*		41*, 42*, 43*	No evidence
Environment functioning	47			No evidence

Numbers in bold print are studies of prospective cohort.
* Australia Melbourne prospective cohort.

memory and impaired verbal working memory were related to lower level of participation at two years post-injury [44].

2) Injury-related factors

Inconsistent evidence was found for severity of injury as predictor of long-term participation. The Australian prospective cohort and two cross-sectional studies [46, 47] examined severity of injury based on the Glasgow Coma Scale (GCS) measured at the emergency department. In the prospective Australian cohort moderate/severe injury had less age-appropriate levels of participation than children with mild TBI at six months post-injury [40, 41]. This relation was not found, in the same cohort, at one or two years post-injury. Shultz et al. found that severe injury leads to more participation problems than complicated mild or moderate TBI at a mean of 2.7 years post-injury [46]. Wells et al. found no relation between severity of injury based on GCS, but they found a relation between more severe injury based on clinical team rating and less participation at 10 years post-injury, describing a young population with a mean age of 5.3 years at injury [47].

Table 2.7 Predictors or associations of health-related quality of life measured with PedsQL in children and adolescents with TBI

Study	6 m	1 y	2 y	≥3 y
USA Washington Prospective cohort				
1. Rivara 2011 [48]		Moderate and Severe TBI* (GCS) Baseline QoL score	Moderate and Severe TBI* (GCS) Less household income Baseline QoL score	
2. Swanson 2012 [49]		Intracranial injuries (CT-scan), especially midline shift ≥5 mm		
3. O'Connor 2012 [50]		PTSD scores at 3 m associated with school and physical functioning Depression scores (PHQ-9) at 3 m associated with school functioning	PTSD scores at 3 m associated with school and physical functioning Depression scores (PHQ-9) at 3 m associated with school functioning	
4. Rivara 2012 [51]				Moderate TBI*
5. Jiminez 2013 [52]		Ethnicity (Hispanic vs NHW)	Ethnicity (Hispanic vs NHW)	Ethnicity (Hispanic vs NHW)
6. Zonfrillo 2014 [53] (mTBI)		Less parental education (some college vs post-college) Low household income Medicaid insurance (medicaid vs private) Sleep problems and pain symptoms at 3 and 12 m		
Europe UK Bristol Prospective cohort				
7. Calvert 2008 [55]	Discharge disability			

Table 2.7 *Continued*

Study	6 m	1 y	2 y	≥3 y
*USA 4 states** Prospective cohort*				
8. McCarthy 2006 [56]		Severe and moderate injury Upper Extremity fracture Pre-psychosocial conditions Poor family functioning Medicaid coverage or being uninsured Single-parent households		
Australia Melbourne Cross-sectional				
9. Green 2013[a] [54]				Psychosocial reintegration Severe vs mild/moderate
Europe UK Cross-sectional				
10. Limond 2009 [57]				Healthcare services
Australia Melbourne Cross-sectioneel				
11. Di Battista 2014[b] [58]				Post-injury depression (self-reported)

PedsQL, Pediatric Quality of Life; TBI, Traumatic Brain injury; GCS, Glasgow Coma Scale; m, month; y, year; PTSD, Posttraumatic stress disorder; PHQ-9, Patient Health Questionnaire; NHW, Non-Hispanic White.
* Compared to reference group (arm injury); ** 4 states (Maryland, Pennsylvania, Washington, Arkansas); [a] Time since injury 13–16 y; [b] Time since injury 2–11 y.

3) Socio-environmental factors

No evidence was found for socio-environmental factors as predictors of long-term participation. Four studies of the same (Australian) prospective cohort [40–43] examined family functioning by using the Family Assessment Device (FAD) in relation to participation: less family functioning pre-injury was related to reduced participation at six months post-injury. This relation was not found, in the same cohort, at one year or two years post-injury.

Overview of factors related to HRQoL by category

Significant factors associated with HRQoL more than six months after injury are described in Table 2.7 and the evidence for the prognostic value is described in Table 2.8.

1) Child specific factors

Child demographics: Weak evidence was found for no association between age and long-term HRQoL [48, 49, 51–53, 58]. No evidence was found for gender or ethnicity as predictors of HRQoL [48, 49, 51–53]. In one study reduced HRQoL was found in Hispanic children versus non-Hispanic white children at one, two and three years post injury [52].

Child function factors: No evidence was found for pre-injury HRQoL as predictor for long-term post-injury HRQoL. This predictor was studied in three studies of the same cohort with inconsistent results [48, 49, 51]. Inconsistent evidence was found for pre-injury mental health problems as predictor for long-term HRQoL [50, 56]. O'Connor et al. found no association between pre-injury mental health problems and long-term HRQoL in adolescents with TBI compared to children with an arm injury [50]. McCarthy et al. found, as only patient characteristic, a significant relationship between pre-injury psychosocial conditions and reduction in all dimensions of HRQoL [56]. Weak evidence was found for no association between pre-injury physical comorbidities as predictor for long-term HRQoL, but in the study of McCarthy et al. this relation was close to significance [53, 56]. Inconsistent evidence was found for post-injury depression as predictor of long-term HRQoL. Three studies examined this relation [50, 53, 58] and one study [50] found a relation between depression scores post-injury at three months and school functioning at one and two years post-injury and another study [53] found no association between depressive symptoms and HRQoL in children with mTBI. The third study, in a small group of adolescents, found a relation between self-reported depression and reduced HRQoL at 2–11 years post injury [58].

Table 2.8 Overview of the evidence for the prognostic value of factors concerning health-related quality of life

Variable	Positive association	Negative association	No association	Evidence
Child demographics				
Age			**48***, **49***, **51–53***, 58	Weak evidence
Gender			**48***, **49***, **51–53***	No evidence
Ethnicity	**52***		**51***, **53***	No evidence**
Child function factors				
Pre-injury QoL		**48***	**49***, **51***	No evidence
Pre-injury mental health		**56#**	**50***	Inconsistent
Pre-injury physical comorbidities			**53***, **56#**	Weak evidence
Post-injury discharge disability	**55^**			No evidence
Post-injury PTSD		**50***	**53***	No evidence
Post-injury depression		**50***, 58	**53***	Inconsistent
Post-injury sleep problems and pain symptoms		**53***		No evidence
Post-injury psychosocial reintegration	54			No evidence
Post-injury anxiety		58		No evidence
Post-injury loneliness		58		No evidence
Post-injury intelligence		58		No evidence
Injury-related factors				
Severity		**48***, **49***, **51***, 54, **56#**	**50***, **52***, **55^**, 57, 58	Inconsistent
Intracranial injuries		**49***		No evidence***
Comorbidities		**56#**	**49***	Inconsistent
Mechanism of injury			**50***	No evidence
Admission to Intensive Care			**50***	No evidence
Socio-environmental factors				
Socio-economic status	**48***, **53***		**50–52***, 57	Inconsistent
Family functioning	**56#**		**48***, **50–53***	Inconsistent
Parental education	**53***		48*, **50*–52***	No evidence
Health insurance	**53***, **56#**		**52***	Inconsistent
Parental marital status	**56#**		**50***	Inconsistent
Health care services	57			No evidence

Numbers in **bold** print are studies of prospective cohort. QoL, Quality of Life.
* USA Washington prospective cohort.
^ Europe UK Bristol prospective cohort.
# USA 4 states prospective cohort.
** Study of Jimenez et al. [52] specifically studied ethnicity by comparing two groups of different ethnicity.
*** Study of Swanson et al. [49] specifically studied intracranial injuries by comparing two groups respectively normal and abnormal CT-scan.

2) Injury-related factors

Inconsistent evidence was found for severity of injury as predictor for long-term HRQoL. In five studies (three of the same cohort) a relation between severity of injury and reduced HRQoL was found [48, 49, 51, 54, 56]. and in five studies (two of the same cohort) no association was found [50, 52, 55, 57, 58]. This inconsistent evidence seemed not to be based on difference in definition of severity of injury, because most studies used the GCS measured at the emergency department. Two studies found that sustaining a moderate or severe TBI was related to lower HRQoL scores at one year post-injury compared to mild TBI [48, 56]. One of these studies found the same relation at two years post-injury [48] and two other studies found this relation at three years post-injury [51, 54]. Swanson et al. specifically studied intracranial injuries by comparing two groups with respectively normal and abnormal CT-scan and found that children who had intracranial injuries, identified on the initial head CT, had significantly lower HRQoL scores compared to children whose initial head CTs were normal [49]. Inconsistent evidence was found for injury-related comorbidities as predictor for long-term HRQoL [49, 56]. One study found a relation between upper extremity fracture and reduced HRQoL at one year post-injury [56].

3) Socio-environmental factors

Inconsistent evidence was found for socio-economic status, family function, health insurance and parental marital status as predictors for long-term HRQoL. No evidence was found for parental education as predictor for long-term HRQoL. Six studies (five of the same cohort) examined the relationship between household income and long-term HRQoL [48, 50–53, 57]. One study found a relation between less household income and reduced HRQoL at two years post-injury [48]. Another study including children with mild TBI found a relation between low household income and reduced HRQoL at one year post-injury [53]. The same study found a relation between less parental education (examined in five studies) and reduced HRQoL and this study found also a relation between Medicaid insurance (instead of private insurance) and reduced HRQoL. In the prospective cohort of Washington no association between family function and long-term HRQoL was found, but in another cohort of the USA a significant relation between less family function and reduced HRQoL was found at one year post-injury [56]. This study found also a relation between Medicaid coverage or being uninsured and reduced HRQoL at one year post-injury. These insurance problems seemed to be related to the cohorts of the USA and not in the countries with good basic healthcare systems.

DISCUSSION

This systematic review has summarized the results of 19 articles on 11 cohorts concerning potential prognostic factors on long-term restrictions in participation and reduced HRQoL in children and adolescents with TBI. Overall, the methodological quality of the included studies was high. Due to heterogeneity of prognostic factors we performed a qualitative analysis.

Potential prognostic factors were divided into three categories: 1) child-specific (child demographics and child function) factors, 2) injury-related factors, and 3) socio-environmental factors. In all categories, significant predictors were found for long-term (≥ six months post-injury) participation and HRQoL.

Participation

Most studied determinants in relation to long-term participation were age at injury, post-injury cognitive functioning, severity of injury and family functioning.

Inconsistent evidence was found for age at injury. Only one cross-sectional study found a significant relation between younger age at onset and reduced participation after 10 years [47]. In this study younger children were included (mean age 5.3 years) compared to the other included studies. This finding is in agreement with Anderson et al. who state that TBI under the age of three years may be more detrimental to ongoing development compared to older children [10]. Several studies not included in this review confirmed age as predictor for adaptive functioning at six months post-injury [30–32]. At 30 months post-injury adaptive functioning was explained by a combination of age at onset and injury severity [30]. In the literature, the prognostic value of age at injury seems to depend of studied outcome whereas interruption of development and/or maturation of the brain play a role [59].

In two studies of the prospective Australian cohort more pre-injury social and behavioral problems were associated with reduced participation at six months and one year post-injury [41, 42]. This is in agreement with previous literature studying the same topic but not included in this review [36, 60].

Strong evidence was found for post-injury cognitive function problems in relation to more restrictions in more than one dimension of participation. Post-injury cognitive functioning problems (slower processing speed, memory problems and executive function problems) were related to reduced participation. This is also in agreement with previous literature, studying post-injury cognitive functioning problems in relation to adaptive functioning on long-term [31].

Inconsistent evidence was found for severity of injury and reduced long-term participation. In the prospective Australian cohort severity of injury was found as predictor for participation at six months post-injury but this relation was not found at two years post-injury suggesting that with time, injury factors are less important contributors for participation. On the other hand, several studies found a significant relationship between injury severity and adaptive abilities or cognitive functioning, and subsequent influence on participation (see above) [31, 61]. Previous research discussed the limitations of only using the GCS at the emergency department in assessing severity of injury [47, 62]. There is evidence that also the duration of loss of consciousness and/or the duration of post-traumatic amnesia (PTA) have a predictive value for post-injury cognitive functioning [61, 63]. Also number and volume of lesions between two and eight weeks post-injury on susceptibility weighted imaging is described as an important prognostic factor for reduced adaptive functioning in children with TBI, especially when located in the frontal lobe [29, 64]. Recent studies suggested that sub-acute microstructural changes in white matter might present a useful prognostic marker for longer term cognitive functioning in children with TBI [65–67].

Not enough evidence was found for associated socio-environmental factors, in contrast to findings in previous studies, not included in this review [31, 68, 69]. Durber et al. found that family environment was related to long-term participation outcome in pediatric TBI [69]. For example higher quality of home environment was associated with better academic/ school performance of the child. In relation to children with orthopedic injuries, children with TBI scored lower on participation and this was even worse when there was lower quality of family functioning [68, 69]. The latter studies thus do suggest that poor socio-environmental factors can even worsen the impairments associated with pediatric TBI, which could lead to poor participation on the long-term in this particular group.

Health-related quality of life

Most studied determinants were age at injury, severity of injury, socio-economic status and family functioning. The heterogeneity of studied predictors of HRQoL do not allow firm conclusions.

Regarding child demographics, weak evidence was found that age at injury is not related to long-term HRQoL and no evidence was found for an association between gender or ethnicity and HRQoL. This is in agreement with previous literature using other outcome measurements than the PedsQol [27, 34, 37]. Regarding child functioning, weak evidence was found for no association between pre-injury physical comorbidities and long-term

HRQoL and inconsistent evidence was found for pre-injury mental health problems and post-injury depression in relation to HRQoL.

Inconsistent evidence was found for injury-related comorbidities and severity of injury in relation to HRQoL. GCS score in combination with or without abnormalities on CT-scan was mostly used to divide in mild, moderate and severe injury. In other prospective cohorts, studying the same topic using other outcome measurements, a relation between higher severity of injury and lower HRQoL was found influenced by time of assessment or kind of reporter [27, 34, 37]. Brown et al. found that children with moderate-severe TBI generally experienced lower HRQoL than children with mild TBI but this difference disappeared by 18 months post-injury [34]. Stancin et al. found that children with severe TBI had lower HRQoL scores four years post-injury based on parent reports but not based on adolescent reports [27]. In this review mostly parent reports were used, just in one study patient reports were used [58]. Previous research demonstrated that parents and children evaluated their HRQoL differently, also in other causes of acquired brain injury. In general, parents gave less optimistic HRQoL scores than their children [6, 70].

Inconsistent evidence was found for socio-environmental factors. However, in previous studies not included in this review, because of using other HRQoL outcome measurements, was found that a better environment helps to moderate the consequences of TBI [27, 34, 37].

In conclusion, restrictions in participation and reduced HRQoL occur at long-term, i.e. several months or years post-injury. In addition, it has been found that adaptive behavior function decreases when demands on the child increase and worsens overtime and subsequent influence participation and affect HRQoL [71, 72].

Strengths and limitations

Because of limited number of studies and participants it was not possible to do a reliable meta-analysis. Overall, the psychometric properties of the instruments used measuring participation and HRQoL were of good validity and reliability.

Publication bias might have occurred in this systematic review. One cohort is used for publishing four articles using different determinants and time points to predict participation. Another cohort is used for publishing six articles using different determinants and time points to predict HRQoL. A few studies used univariate analysis, so the results can be overestimated. Overall, the methodological quality of the included studies was high.

Selection bias may have occurred because all participants visited the emergency department or were inpatients in a study hospital (and discharged alive) or in a rehabilitation

center, so children and adolescents who have visited the family doctor or did not seek medical attention at all could not be taken into account.

Finally, although in this study participation and HRQoL were separately evaluated, these constructs show overlap and it may prove difficult to make clear distinctions between both.

Recommendations and conclusion

The consequences of pediatric TBI may last and evolve over many years and even lifelong. Adequate long-term care requires long-term integrated care pathways. In view of efficient and effective healthcare and scarcity of resources it is pivotal to identify subjects at risk of unfavorable long-term outcome at an early stage. However, no definite conclusions can be drawn from studies published so far. Long-term prospective studies combining multiple child-specific, injury-related, and socio-environmental factors to predict participation outcome and HRQoL at multiple endpoints are pivotal. Therefore, there is a need for a consensus on a core set of child-specific, injury-related and socio-environmental predictors and routine outcome measures. This requires a tracking system that allows secure data collection in which different organizations share measurement tracks involving both patients and professionals.

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APPENDIX 2.1

Search strategy

((Participation[tiab] OR "quality of life"[tiab] OR activit*[tiab]) AND (traumatic brain injury[tiab] OR acquired brain injury[tiab]) AND (("Interpersonal Relations" [majr] OR relationship* OR "Environment" [majr] OR "Social Adjustment" [majr] OR "Patient Participation" [majr] OR social participation [mesh] OR functioning OR recovery of function[mesh] OR education [mesh] OR education* OR health services for persons with disabilities [mesh] OR mobility OR performanc* OR leisure OR "community integration" OR "Activities of Daily Living" OR activities of daily living [mesh] OR "daily life" OR "daily living" OR "Human activities" [majr]) OR QoL OR "Quality of Life/psychology" [Mesh] OR patient acceptance of healthcare [mesh] OR patient satisfaction [mesh] OR "life satisfaction" OR personal satisfaction [mesh] OR "personal gratification" OR "well being") OR (participation NOT (Consumer Participation [mesh] OR "Patient Participation" [mesh] OR "Refusal to Participate" [mesh] OR "patient participation" OR "consumer participation" OR "client participation")) AND ("brain contusion" OR contusion cerebrum OR concussion OR "brain trauma" OR "skull trauma" OR coup-contrecoup brain injury OR mild traumatic brain injury OR moderate traumatic brain injur* OR severe brain injury OR "brain damage" OR craniocerebral trauma OR head injur* OR head trauma OR closed head injur* OR open head injur* OR "intracranial lesion*" OR penetrating head injur* OR "posttraumatic brain swelling" OR brain injur* OR "post concussion syndrome" OR diffuse axonal injur* OR brain laceration*) AND (child [mesh] OR child OR children OR paediatric OR pediatric OR infant* OR childhood OR kid OR preteen* OR pubescent OR adolescent[mesh] OR adolescent* OR adolescence OR young adult* OR young adult [mesh] OR teenage* OR teen* OR juvenile OR youth* OR youngster OR girl OR schoolgirl OR boy OR schoolboy OR boyhood OR girlhood))

Chapter 3

Neurological outcome in children and youth with acquired brain injury two years post-injury

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Abstract

Objective: To determine neurological outcome in children and youth with acquired brain injury (ABI) and explore associated factors.

Design: Cross-sectional study, two-years post-injury. Patients: hospital-based sample (n=112) aged 6–22 years.

Methods: Neurological outcome and participation were assessed with a multidimensional neurological examination and the Child and Adolescent Scale of Participation. Logistic regression analyses were used to explore the relationships.

Results: Both sensorimotor and cognitive deficits were found in 30–31%, language deficits and behavioural deficits in 10–17%. Non-traumatic injury had a negative impact on neurological outcome, specifically regarding sensorimotor and language deficits. Lower education level showed a significantly poorer neurological outcome. High levels of age-expected participation were reported, with a significant relation between deficits and participation restrictions, especially at school.

Conclusion: One out of three have a poor neurological outcome, related to type of injury and lower level of education. The amount of deficits is associated with participation restrictions.

INTRODUCTION

Acquired brain injury (ABI) refers to any damage to the brain that occurs after the neonatal period. Brain injury due to trauma (traumatic brain injury, TBI) is the most common cause and other causes (non-traumatic brain injury, nTBI) are tumours, epilepsy/post-anoxic encephalopathy, stroke, encephalitis/ meningitis and demyelinating diseases [1]. In first-world nations ABI is a leading cause of morbidity and mortality in children and adolescents [2]. In the Netherlands, the estimated yearly incidence rates are substantial for the age group 0–24 years, i.e. for TBI 585 per 100,000 and for nTBI 190 per 100,000, of whom 10–15% is classified as moderate or severe [3].

Diffuse pathology caused by brain injury may have more serious and persisting consequences in children than in adults due to the immaturity of the young brain and the risk to disrupt ongoing brain development [4, 5]. Since multiple neural systems may be involved, this results in a large variety of consequences, affecting motor [6, 7], communication [8, 9], cognitive [10–12] and behavioural functions [10, 13, 14]. Outcome on the long term (at least 1 year post-injury), have received limited attention and remain poorly understood, particularly for children with mild injury. Clinical perceptions of long-term outcome may be negatively skewed, with only those children with severe and persisting problems presenting for healthcare services in the chronic phase. Prediction of long-term outcome after pediatric ABI may help to monitor vulnerable patients, and to optimise the use of scarce resources in long-term treatment planning. Global multidimensional or domain-specific outcomes have been used for children and youth with ABI and TBI [15, 16]. In addition, clinical screening of potential sensorimotor, language, cognitive or behavioural deficits is necessary to determine and monitor long-term neurological outcome after ABI and set priorities for treatment and follow-up.

The complex interaction between neurological deficits and its consequences in various domains of functioning can be understood using the International Classification of Functioning, Disability and Health for children and Youth (ICF-CY) [17]. Consequences of ABI may include limitations of daily activities and participation restrictions. Participation refers to a person´s involvement in meaningful life situations in several settings. After ABI, limitations in activities are assumed to have considerable impact on children's participation at home, school and in community life [18, 19]. There is little evidence to confirm if children and youth with deficits after ABI on the long term function at the same level as their peers. Studies about relationships between neurological deficits and participation in this population are limited, so more insight in these relationships is needed.

Therefore, this cross-sectional study at two years post-injury investigated the consequences of paediatric ABI in a hospital-based cohort, addressing neurological outcome and its correlations with sociodemographic and injury-related characteristics. In addition, associations of neurological outcome with activity limitations and participation restrictions were explored. Based on literature [20] and from clinical experience, we hypothesised that neurological outcome would be poorer for children: i) with more severe ABI [8, 21]; ii) with younger age at onset [4, 19]; iii) with pre-injury developmental problems [22, 23]; and iv) for children from families with a lower socioeconomic status (SES) [24, 25]. Moreover, it was expected that poorer neurological outcome would be related to more activity limitations and participation restrictions [26].

METHODS

Participants

This study was part of a larger cross-sectional two-year follow-up study on outcome after ABI in children and youth (aged 6–22 years) living in the Netherlands [3, 27]. A stratified

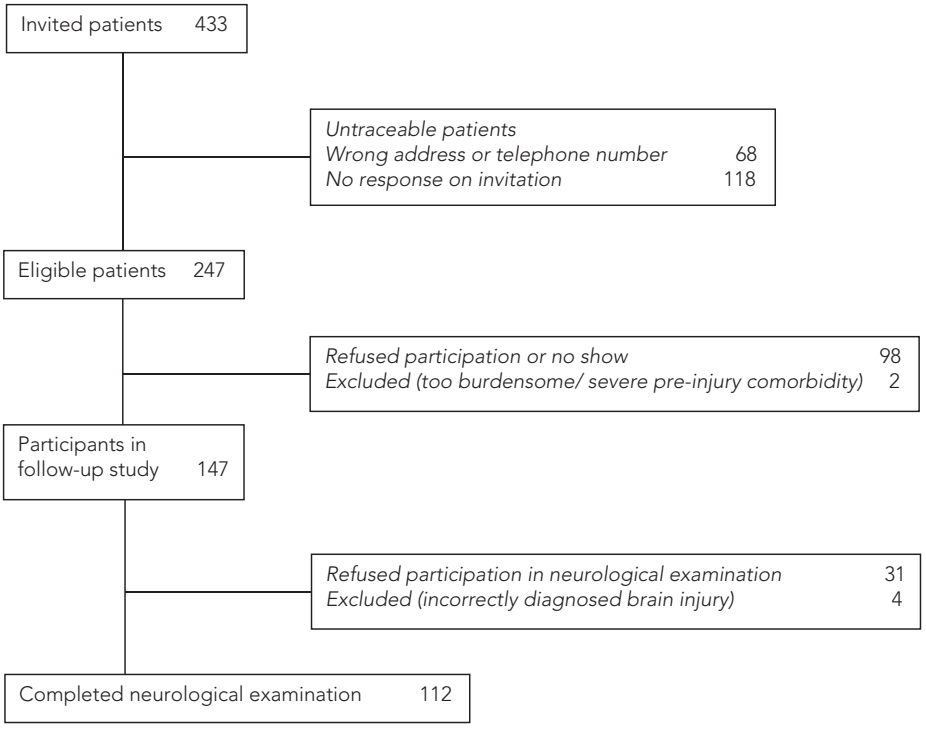

Figure 3.1 Flow chart of the patient recruitment process.

sample was drawn from a multi-centre incidence cohort of 1892 patients with a diagnosis of ABI, acquired in 2008 or 2009, from large tertiary care hospitals in the south-western region of the Netherlands. The sample was stratified for year of onset (2008; 2009), type of injury (TBI; nTBI), severity of injury (mild; moderate; severe) and age at onset (4–12 years; 13–20 years). Criteria for traumatic brain injury were: a history of observed loss of consciousness after a head trauma, and/or symptoms related to brain injury, and/or the presence of post-traumatic amnesia, and/or abnormalities at neurological examination, and/or acute traumatic abnormalities on scan images of the brain. Severity of TBI was based on the Glasgow Coma Scale (GCS) at time of presentation in the emergency room (mild GCS 13–15, moderate GCS 9–12, severe GCS <9) [28, 29]. Severity of nTBI was classified using the modified paediatric Ranking Scale (mRS), assessed at discharge from the hospital (mild mRS 0–1, moderate mRS 2–3, severe mRS 4–5) [10, 30, 31].

An invitation to attend a 2-year follow-up assessment was sent to 433 patients; of these, 247 potential participants were traceable (Figure 3.1). No reply was largely due to inaccuracies regarding the patients' addresses. Of the 247 eligible patients, 147 (60% response rate) consented to participate; two other patients were excluded since the physical, mental or emotional effort of the study was considered to be too burdensome, or due to severe physical pre-injury comorbidity (cerebral palsy). Participants (n=147) and non-participants did not differ regarding gender or type of injury, but relatively more young patients (4–12 years at onset ABI) participated (57% vs. 48%, p=0.02) as well as more patients with a severe injury (9% vs. 3%, p=0.02).

Out of the 2-year follow-up cohort, 112 participants completed the neurological examination; 31 patients refused to participate in this part of the study; four patients were excluded after the assessment: two with trauma capitis (minor head injury without brain symptoms) and two patients with a psychogenic disorder that was initially diagnosed as nTBI. Dropout for this part of the study was not selective for age, gender, type or severity of injury. All participants and/or their parents gave written informed consent to participate. The study was approved by the Medical Ethical Committee (MEC) of the Erasmus University Medical Centre Rotterdam (MEC-2009-440).

Procedure

In this part of the study, participants were assessed in an outpatient clinic of the participating hospitals. A standardized neurological examination was performed by medical doctors (residents in Rehabilitation Medicine), who are trained to perform a full neurological examination. Prior to the examination, parents filled in the Child and Adolescent Scale

of Participation (CASP) [32] and parents were questioned about the medical history of their child and asked to indicate the presence of pre-injury developmental problems. Participants were informed about the results of the assessment and were referred to a medical specialist in Rehabilitation Medicine when indicated.

Measurements

Primary outcome measure

Based on a literature search and consultation of paediatric neurologists we selected a comprehensive and multidimensional examination to screen and quantify neurological deficits that can be completed in a feasible time. The extended paediatric neurological examination was standardized according to the *Paediatric Stroke Outcome Measure Short Neuro Exam* (*PSOM*) to assess neurological function [9, 11, 31, 33, 34]. The neurological examination includes 115 items, addressing right and left sensorimotor function, language production, language comprehension, and cognitive/behavioural function. The participant was examined directly, using specific tasks, such as a counting task, a drawing task or a memory task to assess cognitive functions, or the examiner's judgment whether the child's interpersonal interaction and cooperation during the assessment were age-appropriate. Due to lack of adequate proficiency, the examiners did not perform ophthalmoscopy; instead we measured visual acuity at a distance of 5 meters (deficit when <0.8). All items are listed in Appendix 3.1.

In the present study in patients with ABI, we combined right and left sensorimotor deficits (subscale 1 and 2) into one domain of sensorimotor deficits, and scores on language production and comprehension (subscale 3 and 4) were combined into one domain of language deficits. The results of subscale 5 were split into two separate domains representing cognitive and behavioural deficits. Similar to the PSOM, these domains were scored as 0 (no deficits) 0.5 (mild deficit that does not interfere with function), 1 (moderate deficit that interferes with function) and 2 (severe deficit); also an overall neurological deficit score was calculated, with levels indicating normal, mild, moderate or severe deficits (see Appendix 3.1) [9].

Associated factors

We studied the following variables as possible factors associated with neurological outcome: 1) sociodemographics: age (y), sex (girl/boy) and ethnicity (Dutch/non-Dutch origin); 2) injury-related variables: type of injury (TBI/nTBI) and severity of injury (mild versus moderate/severe); 3) level of functioning: current education level of the child (low, intermediate, high) and pre-injury developmental status of the child (presence of motor,

language/speech, cognitive/learning, social/emotional problems: no/yes); and 4) family-related variables: family situation (single-parent versus two-parent family) and SES of the parents, which was estimated from the highest educational level achieved by of one of the parents (low versus intermediate/high).

Parents or caregivers reported on activity limitations and participation restrictions using the CASP. The CASP is a part of the Child and Family Follow-up Survey (CFFS) and is developed to assess long-term outcomes in young people with ABI. McCauley et al. [16] has recommended that the CASP be considered as a supplemental measurement to determine social role participation. The CFFS has been translated and adapted into a Dutch language version and has shown adequate reliability/validity to measure long-term outcomes of children and youth with ABI in the Netherlands [35].

The CASP measures activity limitations and participation restrictions compared to same-age peers. The CASP consists of 20 ordinal scaled items divided into four life areas: 1) home participation, 2) school participation, 3) community participation, and 4) home and community living activities. The items are rated on a 4-point scale (4=age expected, 3=somewhat limited, 2=very limited, 1=unable); in addition, an item can be rated as 'not applicable'. CASP summary scores (total score and 4 sections) are calculated and transformed to a 0–100 scale, excluding non-applicable items. Higher scores indicate a greater extent of age-expected participation [32].

Statistical/data analysis

Descriptive statistics for the results of neurologic outcome were computed, addressing the four domains of neurological deficits and the overall neurological deficits score. None or mild neurological deficits on the overall score were considered as good outcome, and moderate or severe deficits as poor outcome [9].

To explore associations of patient and injury-related characteristics with neurological outcomes at 2-year post-injury we performed logistic regression analyses separately for overall neurological outcome and each of the four domains of neurological outcome: sensorimotor deficits, language deficits, cognitive deficits and behavioral deficits. For these analyses we dichotomized neurological outcomes as normal versus presence of deficits (mild to severe); associated factors studied were a continuous variable (age), and other variables in two levels, except for education level (3 levels). Analyses were performed in three steps. First, we explored significantly related factors by means of univariable logistic regression analyses. Second, basic models were tested for age and the univariable significant factors: educational level and type of injury. Third, multivariable analyses were

performed entering an additional factor on pre-injury functioning or ethnicity one at a time, in order to analyse the relation of neurological outcome with these univariably significant factors while adjusting for age, educational level and type of injury. Thus, we limited the number of independent variables in a model to a maximum of 4, to accommodate for sample size. In a similar way we tested multivariable models for the relation between neurological outcomes and participation restrictions one at a time, while adjusting for educational level and type of injury; the latter models were not adjusted for age, since participation restrictions were assessed age-appropriately. CASP scores were dichotomized at 100 (which was the median score in all sections and summary scores), referring to age-expected participation (score 100) versus some restriction (score <100). All data were analysed using SPSS for Windows version 21.0.

RESULTS

Sample

Table 3.1 presents the characteristics of the present sample (n=112); mean age was 13.0 ± 4.9 years and 63 were boys (56.3%).

Brain injury was traumatic in 86 participants (76.8%). Half of the nTBI was due to a brain tumour (n=14). Other causes were epilepsy/post-anoxic encephalopathy (n=4), stroke (n=3), encephalitis (n=2), meningitis (n=1) and demyelinating disease (n=2).

Severity of TBI was mild in 76 (88.4%) and moderate/severe in 10 participants (11.6%). In nTBI severity was mild in 20 (76.9%), moderate/severe in four (15.4%) and unknown in two participants. In 57 participants (50.9%) current level of education was low, including elementary school.

Parents indicated pre-injury developmental problems in motor function in 11 (9.8%) participants, problems in language/speech in eight (7.1%), cognition/learning problems in 14 (12.5%), and social-emotional problems in 14 participants (12.5%). More specifically, in participants with a brain tumour (n=14), pre-injury motor problems were indicated by four parents, problems in language/speech by two parents, cognition/learning problems and social-emotional problems by one couple of parents. Thus, the percentage of pre-injury motor problems in participants with a brain tumour was relatively high; these problems may have been the first symptoms indicating the presence of a tumour.

The sample showed mean scores ≥92.4 on the total CASP score and the first three subsections, whereas a mean score of 86.1 was found for activities at home or for the

Table 3.1 Characteristics of the 112 participants

	Values n (%)	Missing n
Sociodemographic		
Age (years)		0
Mean (SD): 13.0 (4.9)		
6–10	43 (38.4)	
11–16	38 (33.9)	
17–22	31 (27.7)	
Sex		0
Girls	49 (43.8)	
Boys	63 (56.2)	
Ethnicity		4
Dutch	79 (70.5)	
Non-Dutch origin	29 (25.9)	
Injury related		
Type of injury		0
TBI	86 (76.8)	
nTBI	26 (23.2)	
TBI severity		0
Mild	76 (88.4)	
Moderate/severe	10 (11.6)	
nTBI severity		2
Mild	20 (76.9)	
Moderate/severe	4 (15.4)	
Level of function		
Current education level		9
Elementary school or junior vocational	57 (50.9)	
Secondary vocational	23 (20.5)	
Secondary general high	23 (20.5)	
Pre-injury developmental problems		
Motor function	11 (9.8)	4
Language/speech	8 (7.1)	4
Cognition/learning	14 (12.5)	4
Social-emotional	14 (12.5)	3
Family related		
Family situation		8
Single-parent family	31 (27.7)	
Two-parent family	73 (65.2)	
Family socio-economic status		11
Low*	12 (10.7)	
Intermediate/high**	89 (79.5)	
Level of participation	*Mean (SD)*	11
CASP total score (range 0–100)	92.4 (11.4)	
Home participation	96.8 (7.9)	
Community participation	93.8 (12.8)	
School participation	94.7 (12.8)	
Home & community living participation	86.1 (20.6)	

TBI, traumatic brain injury; nTBI, non-traumatic brain injury; CASP, Child and Adolescent Scale of Participation; * No education or primary school; **Secondary school or higher education.

neighbourhood (activities for independent living). Age-appropriate participation was restricted in 42% of the sample, with 25–29% of the sample experiencing participation restrictions at home, community and school, and 50% restrictions in home and community living activities.

Neurological outcome

Table 3.2 shows the overall neurological outcome for the total sample and for subsamples (nTBI, all TBI, moderate/severe TBI and mild TBI). There was a significantly poorer outcome for participants with nTBI as compared to TBI (OR 6.6; 95% CI 1.8–24.6). In the group with nTBI 31% of children and youth had a better outcome and 69% a poor neurological outcome. In the TBI group 77% of children and youth had a better outcome (normal or mild deficit) and 23% a poor outcome (moderate or severe deficit). The latter percentages of poor outcome varied between 40% in those with moderate/severe TBI to 21% in mild TBI.

Table 3.2 Deficit Severity Score (DSS) from Pediatric Stroke Outcome Measure (N(%))

DSS	Total sample N=112	nTBI N=26	All TBI N=86	Moderate/ severe TBI N=10	Mild TBI N=76
Good					
Normal	49 (43.7%)	5 (19.2%)	44 (51.2%)	4 (40%)	40 (52.6%)
Mild deficit	25 (22.3%)	3 (11.5%)	22 (25.6%)	2 (20%)	20 (26.3%)
Poor					
Moderate deficit	21 (18.8%)	8 (30.8%)	13 (15.1%)	3 (30%)	10 (13.2%)
Severe deficit	17 (15.2%)	10 (38.5%)	7 (8.1%)	1 (10%)	6 (7.9%)

TBI, traumatic brain injury; nTBI, non-traumatic brain injury.

Deficits in specific domains of neurological outcome are shown in Table 3.3. In total, 31.3% of the participants had one or more sensorimotor deficits; 24 participants (21.4%) had bilateral and 11 (9.8%) unilateral sensorimotor deficits. The total sample showed cognitive deficits in 34 (30.4%) participants, language deficits in 11 (9.8%) and behavioural deficits in 19 (17.0%) participants. When excluding the item visual acuity, the proportion of participants with sensorimotor deficits decreased: 15 (57.7%) in the nTBI group, 13 (15.1%) in the total TBI group, and 9 (11.8%) in the mild TBI group.

Table 3.3 Domains of neurological outcome in total sample and subsamples

	Total sample n=112	nTBI n=26	All TBI n=86	Mild TBI n=76
Domain-specific deficit	N (%)	N (%)	N (%)	N (%)
Sensorimotor deficits	35 (31.3%)	16 (61.5%)	9 (22.1%)	15 (19.7%)
Mild	20	7	13	11
Moderate/severe	15	9	6	4
Language deficits	11 (9.8%)	6 (23.1%)	5 (5.8%)	4 (5.3%)
Mild	7	5	2	1
Moderate/severe	4	1	3	3
Cognitive deficits	34 (30.4%)	11 (42.3%)	23 (26.7%)	22 (29.0%)
Mild	23	6	17	16
Moderate/severe	11	5	6	6
Behavioural deficits	19 (17.0%)	5 (19.2%)	14 (16.3%)	14 (18.4%)
Mild	14	3	11	11
Moderate/severe	5	2	3	3

TBI, traumatic brain injury; nTBI, non-traumatic brain injury.

Associated factors

Associated factors for overall and domain-specific neurological outcomes are shown in Table 3.4. The basic models show that type of injury was significantly associated with outcome, i.e. poorer outcome in children and youth with nTBI, specifically regarding sensorimotor and language deficits. Severity of brain injury was not associated with overall or domain specific neurological outcome 2-years post-injury. Overall, children with a lower education level showed a significantly poorer neurological outcome, which applied specifically to cognitive deficits. We found no significant associations for age or other sociodemographic factors (sex, ethnicity) with overall or domain specific neurological outcome in ABI, nor for family factors such as family situation or SES. After adjusting for basic characteristics, pre-injury developmental problems in motor and social-emotional functioning were significantly associated with long-term sensorimotor deficits and pre-injury cognitive/learning problems with long-term language deficits.

Regarding participation, overall neurological outcome and deficits in the specific domains were associated with participation restrictions in several life areas according to the CASP, after adjusting for current education level (Table 3.5). More specifically, long-term sensorimotor, language and cognitive deficits were significantly associated with overall participation restrictions. Sensorimotor deficits were especially associated with participation restrictions at home and at school. Language deficits were especially associated with participation restrictions at school. Cognitive deficits were associated with participation at

Table 3.4 Associated factors for overall and domain-specific neurological outcomes

	Neurological outcome (normal/deficits)		Sensorimotor deficits (normal/deficits)		Language deficits (normal/deficits)		Cognitive deficits (normal/deficits)		Behavioural deficits (normal/deficits)	
Associated factors	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2
Basic models										
Age (y)	1.1 (0.97–1.3)	0.34	1.1 (0.96–1.3)	0.25	1.1 (0.96–1.3)	0.21	1.1 (0.9–1.2)	0.18	1.0 (0.9–1.2)	0.07
Type of injury (TBI/nTBI)	**6.6 (1.8–24.6)**		**6.1 (2.2–16.9)**		**4.5 (1.1–17.5)**		2.4 (0.9–6.6)		1.1 (0.3–3.6)	
Educational level (low/ medium/high)	**0.2 (0.1–0.5)**		0.4 (0.2–1.01)		0.2 (0.04–1.1)		**0.3 (0.1–0.7)**		0.4 (0.2–1.2)	
Adjusted models										
Ethnicity (Dutch/non-Dutch origin)	-		n.s.		-		-		-	
Pre-injury motor problems (no/yes)	n.s.		**7.4 (1.6–35.0)**	0.32	-		-		-	
Pre-injury language/speech problems (no/yes)	-		n.s.		-		-		n.s.	
Pre-injury cognition/ learning problems (no/yes)	-		-		**12.3 (1.9–82.2)**	0.33	-		-	
Pre-injury social-emotional problems (no/yes)	-		**7.1 (1.8–27.5)**	0.34	-		-		-	

OR, odds ratio; CI, confidence interval; R^2, Nagelkerke R square explained variance; n.s., not significant (but significant in univariate model); -, not tested in multivariate model because not significant in univariate model. **Bold** values represent significant relations.

Table 3.5 Relations of neurological outcomes with participation restrictions

	CASP total participation (age-expected/restricted)		Home participation (age-expected/restricted)		School participation (age-expected/restricted)		Community participation (age-expected/restricted)		Home/community living activities (age-expected/restricted)	
Associated factors	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2	OR (95% CI)	R^2
Basic models										
Type of injury (TBI/nTBI)	2.6 (0.9–7.8)	0.23	1.7 (0.6–4.5)	0.10	1.9 (0.7–4.9)	0.09	2.4 (0.9–6.4)	0.13	1.8 (0.3–3.6)	0.26
Educational level (low/medium/high)	**0.4 (0.2–0.6)**		**0.5 (0.3–0.9)**		**0.5 (0.3–0.94)**		**0.5 (0.3–0.9)**		**0.3 (0.2–0.5)**	
Adjusted models										
Overall neurological deficits (normal/deficits)	**3.5 (1.3–9.4)**	0.29	**4.0 (1.3–11.8)**	0.19	**6.6 (2.1–21.0)**	**0.24**	**3.2 (1.1–8.9)**	**0.19**	n.s.	
Sensorimotor deficits (normal/deficits)	**4.1 (1.2–13.7)**	0.29	**4.0 (1.5–10.8)**	0.19	**4.0 (1.5–10.8)**	**0.19**	-		-	
Language deficits (normal/deficits)	-		-		**4.8 (1.1–20.5)**	**0.15**	-		n.s.	
Cognitive deficits (normal/deficits)	**3.6 (1.1–12.2)**	0.28	n.s.		**2.6 (1.0–6.7)**	**0.14**	n.s.		**3.2 (1.1–9.4)**	**0.31**
Behavioural deficits (normal/deficits)	n.s.		**6.3 (2.1–19.3)**	0.24	**3.1 (1.1–8.8)**	**0.15**	**3.0 (1.0–8.8)**	**0.18**	n.s.	

OR, odds ratio; CI, confidence interval; R2, Nagelkerke R square explained variance; n.s., not significant (but significant in univariate model); -, not tested in multivariate model because not significant in univariate model.

school and at home/community living, and behavioral deficits with participation at home, school and in the community. Notably, neither type of injury nor severity of injury were associated with participation restrictions.

DISCUSSION

ABI is a major cause of disability in children and youth and often leads to an interruption in normal development. In the present hospital-based sample one out of three children had a poor neurological outcome 2-years post-injury according to a paediatric neurological examination, with a significantly poorer outcome for children and youth with nTBI (with two out of three having moderate or severe deficits). In addition, the present study added to the evidence that neurological deficits on the long term correlate to participation restrictions in several areas.

In clinical practice, a comprehensive and multidimensional examination gives insight in to several domains. In this study we performed a comprehensive neurological examination, applying standardization and scoring in line with the PSOM Short Neuro Exam, which has originally been developed for studying children with a specific type of ABI, arterial ischemic stroke. At this moment this is the only scoring system based on a detailed neurological examination, which is still considered the gold standard to evaluate neurological deficits [36, 37].

In this study, both sensorimotor and cognitive deficits were found in 30–31% of the children with ABI, whereas a smaller proportion had language and behavioural deficits (10–17%). The percentages of sensorimotor and cognitive deficits are considerably higher than in the general population. As compared with other studies, we detected a relatively high percentage of sensorimotor deficits in mild TBI (19.7%), which may (in part) be due to a strong emphasis on this domain in the neurological examination. When excluding visual acuity (we added this item to the examination), the percentage of sensorimotor deficits in mild TBI decreased to 12%. In mild TBI the most pronounced sensorimotor deficits were found on visual acuity (impaired in 22% right and 13% left), tandem gait (impaired in 5%), and rapid sequential finger movements (impaired in 4%). Some of the detected sensorimotor deficits may have existed pre-injury (clumsiness and vision abnormalities), but may not have been detected previously. On the other hand, it is known that up to more than three months after mild TBI, significantly more balance deficits are present compared to the general population [38, 39].

Children and youth with nTBI and those with lower education levels were at increased risk for poorer overall neurological outcome 2-years post-injury. The finding that type of injury

(non-traumatic) has a negative impact on overall neurological outcome is most likely due to the pathophysiological response causing more diffuse pathology (and deeper) in the brain instead of the more focal pathology in traumatic lesions [20]. The negative impact of a lower education level of the child can possibly be explained from a lower cognitive reserve due to a less efficient utilisation of brain networks or a lower ability to recruit alternate brain networks as needed [40, 41].

In contrast to our hypotheses, severity of brain injury, age at onset and parents' SES did not predict overall neurological outcome in this sample of children and youth with ABI on the long term. On the other hand, pre-injury developmental problems in motor functioning, cognitive functioning and social-emotional functioning were associated with poorer neurological outcome in specific domains. These latter findings are in line with previous studies in which pre-injury problems were measured more objectively [42–44].

Remarkably, severity of brain injury was not related to poorer neurological outcome two years after ABI. This is in contrast to other studies [20] indicating severity of injury as a predictor of sensorimotor, language, cognitive and behavioural problems, although the importance of this factor may vary for different outcomes or for different time periods of follow-up after injury [4, 7, 43, 45]. Specifically, in the (sub)acute post-injury period, severity of injury appears to be a critical predictor for outcome in TBI, but on a longer time after injury also those with severe injury may reach a better outcome [12, 44, 46]. Age did not appear to be a predictive factor for poorer neurological outcome in ABI in this study. This is in line with previous studies in mild TBI [4, 47]. The latter subgroup was actually the largest group in the present study sample. Unexpectedly, the parents' SES did not predict outcome in this study. This might be due to the large percentage (79.5%) of intermediate/high levels of SES in our study population.

In the present study, poorer overall neurological outcome as well as the presence of deficits in the specific domains of functioning were associated with participation restrictions in several life areas, measured with the CASP. Most parents reported high levels of age-expected participation of their child according to the CASP (mean total CASP score 92.4). The presence of long-term neurological deficits after ABI do not always induce participation restrictions, but more deficits and more severe deficits were related to restricted participation. The reported levels of participation appear slightly higher than reported by Bedell [32] who included children with a range of disabling conditions (predominantly ABI) approximately four years post-injury (mean CASP score 85.0) and by Lo et al. [34] (range 70–100) reporting on paediatric stroke approximately six years after onset. Similar to the present study, Lo et al. found that neurological deficits assessed with the total PSOM deficit severity score correlated with poorer age-expected participation (Rs=-0.57). More

specifically, the present results underline the importance of sensorimotor, cognitive and also language and behavioural deficits for age-expected participation in several areas (at home, at school, and in the community). These four domains of neurological deficits were all significantly related to participation at school, probably due to the fact that this environment demands a wide range of skills to participate at the same level of their peers.

Limitations

A large number of patients were not traceable two years after ABI, or did not respond on the invitation for a follow-up assessment. We checked, however, that the present sample did not differ from the target population of children and youth with a hospital-based diagnosis ABI, except for slightly higher percentages of patients under the age of 12 years and those with severe injury. Thus, we assume that the high non-response did not seriously affect the generalizability of the results. In the present study sample, the percentage of mild TBI is high (88%), which is within the range that is generally reported (70–90%) [48]. This may be related to the method of recruitment, which was done using hospital charts at the time of injury; among those children seen at the emergency room a large percentage has mild ABI [3], not requiring further treatment or rehabilitation.

In this study we intentionally investigated a heterogeneous sample of children with ABI comprising both those with TBI and nTBI. Within the broad sample the subsample with nTBI (26 patients) is relatively small, which is however in accordance to current incidence rates. Also, the distribution of type of injury was adequate to enter this factor in the multivariable regression models for neurological outcomes, which confirmed a poorer outcome of those with nTBI.

Two years after brain injury parents were asked to retrospectively report the pre-injury developmental problems of their child. This approach is sensitive to recall bias due to possible inaccuracy in remembering these facts from the pre-injury period; moreover, some 'pre-injury' problems may have been the first symptoms of nTBI. For future studies, we recommend to use more objective measurements (if available) to evaluate pre-injury problems, such as psychological assessments or teacher ratings.

Recommendations

A clinical neurological multidimensional assessment seems to be of essential value to detect and quantify neurological deficits, also two years after injury. Since neurological outcome measures developed for cerebral paediatric disorders (e.g. cerebral palsy) may be insensitive to the more focal and sometimes mild deficits that result from ABI [9], we

are in need of other assessment tools. A standardized method for assessing neurological deficits multidimensional will have a complementary role in addition to the functional outcome scales or domain-specific tests that are presently used for children and youth with ABI and TBI [15, 16]. Recently, the predictive value of the PSOM for functional outcomes including cognitive ability, problem behaviour, adaptive behaviour and social participation has been confirmed [34]. Since such a neurological examination is feasible within one hour, we recommend its use to screen, monitor and quantify sensorimotor, language, cognitive and behavioural deficits in a clinical setting.

In conclusion, in our hospital-based cohort, one out of three children had a poor neurological outcome two years after paediatric ABI, specifically those with nTBI or a lower level of education. In particular, sensorimotor and cognitive deficits were found. nTBI was related to more sensorimotor and language deficits and a lower education level to more cognitive and behavioural deficits. The amount and severity of neurological deficits were associated to level of participation within all areas, especially at school.

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APPENDIX 3.1

Paediatric neurological examination standardized according to the PSOM Short Neuro Exam*

1. SENSORIMOTOR (right and left combined)

CRANIAL NERVES

TEST ITEMS		Guidelines for Scoring and Notes (Describe Abnormalities)
Visual Fields	Right	Facing patient at 2–3 ft encourage to stare at your eyes and tell when they see object come into view from side (or note gaze shifting toward object)
	Left	
Pupillary Light Reflex	Right	Direct and Consensual
	Left	
Visual acuity (adapted item)	Right	*Card (Landolt C) at 5 meters distance* *Abnormal <0.8*
	Left	
Ocular Motility	Right	Move pen or red object or light smoothly from right to left and back testing full range. Watch for nystagmus or dysconjugate eye movements
	Left	
Optokinetic Nystagmus	Right	Move measuring tape slowly from right to left and back through full range encourage to 'watch the numbers as they go by'
	Left	
Facial Sensation	Right	Touch each side with light touch and cold object asking if child can feel or for older, 'is it the same on both sides' comparing forehead, cheek and chin R / L
	Left	
Facial Movements	Right	Ask patient to smile, count to 10 watching mouth symmetry Maximal eye closure strength "*Squeeze eyes shut as tightly as you can*"
	Left	
Hearing	Right	Finger rub for infants or whisper at 2-3 feet away. For older have child repeat letters/numbers
	Left	
Swallow		
Palate and gag	Right	Observe during open mouth crying or Demonstrate with tongue protruded '*Say 'ahhhhh.*" Listen to voice quality
	Left	
Trapezius Strength	Right	Test Shoulder Shrug
	Left	
Tongue Movements Side-To-Side	Right	
	Left	

MOTOR EXAM
POWER, TONE, TENDON REFLEXES AND INVOLUNTARY MOVEMENTS

Neck/Trunk Muscles
Right Arm
Proximal
Distal
Left Arm
Proximal
Distal
Right Leg
Proximal
Distal
Left Leg
Proximal
Distal

Bicepsreflex	Right
	Left
Brachioradialisreflex	Right
	Left
Tricepsreflex	Right
	Left
Knee Jerk reflex	Right
	Left
Quadriceps reflex	Right
	Left
Ankle Jerk reflex	Right
	Left
Babinski reflex	Right
	Left
Elicited ankle clonus	Right
	Left

TYPE	? Present
Limb Tremor	
Choreoathetosis	
Dystonic Posturing	
Tics	

FINE MOTOR COORDINATION

TEST ITEMS		Guidelines for Scoring
Pincer Grasp	Right	Encourage to pick up small 2–3 mm. ball of rolled up paper
	Left	
Rapid Sequential Finger Movements	Right	**Demonstrate**: thumb touches tip of individual fingers back and forth 5 times "*As fast as you can*"
	Left	
Rapid Index Finger Tap	Right	**Demonstrate**: seated, finger taps table top or own thigh X 20 times, "*As fast as you can*"
	Left	
Finger To Nose Testing	Right	
	Left	
Heel To Shin Testing	Right	
	Left	
Rapid Foot Tap	Right	**Demonstrate**: feet flat on floor, foot taps floor X 20 "*As fast as you can*"
	Left	
Sitting/Standing Balance		

SENSORY

TEST ITEMS		Guidelines for Scoring
Light Touch	Right	Use cotton swab and **ask**: "*Is it the same on both sides?*"
	Left	
Pin Prick or Cold Sensation	Right	Use cool metal from tuning fork or reflex hammer
	Left	
Proprioception	Right	Great Toe up and down with eyes closed (**ask**: "*up or down?*")
	Left	
Graphesthesia/ Stereognosis	Right	Test >6 yrs: Eyes closed, draw number in palm & foot dorsum with closed pen tip
	Left	

GAIT

TEST ITEMS		Guidelines for Scoring
Gait Walking		By ≥16 mos.
Gait Running		By 2 yrs age
Gait on Heels		
Gait on Toes		10 steps
Tandem Gait		Heel to toe: test > age 6 yrs; walk on line forward (10 steps)
Jump on 2 Feet		By ≥36 mos.
Hop on Foot Repetitively	Right	25 x (*age 7 yrs to 9 yrs*) 50 x (*age 9 yrs or older*)
	Left	
Station on one leg sustained	Right	Test age 7 and up. Count seconds out loud and compare stability.
	Left	
Romberg's Sign		"*Eyes closed, feet together, arms stretched forward*".

2. LANGUAGE (production and comprehension combined)

TEST ITEMS	Guidelines for Scoring
Speech Development	**Normal**: **2 years** – 2 word phrase **3 years** – 3 word sentence, 200 words **4 years** – more word sentences Age-dependent
Repetition	"*Stop*"; "*Stop and Go*"; "*If it rains we play inside*"; "*No ifs ands or buts*" "*The Prime Minister lives in Ottawa*" (or local version!)
Naming	Show patient attached sheet with pictures: skateboard, pencil, shirt, bicycle, and clock. Children ≥6 yrs ask to identify: pencil, eraser, bicycle seat, buttons
Comprehension	**Simple Tasks**: a. *Close your eyes* b. *Touch your nose* c. *Point to the floor and then ceiling* **Complex 3 Step Command**: ask child to listen to the complete instruction, remember it, then do all 3 activities together when prompted: "*Blink twice, stick out your tongue, then touch your finger to your nose*"
Letter Recognition/Reading	Ask patient to identify letters A, B, H
Writing	Ask patient to print first name (age 5–7) first and last name (age 8–9) or write first and last name in cursive

3. COGNITIVE (separate domain)

TEST ITEMS	Guidelines for Scoring
Level of Consciousness	
Attention	**Abnormal**: Short, distractible, flits, ignores, preoccupied, disorganized, inattentive
Serial Numbers	Age **4–8** yrs: **Ask**: "*Start at 20 count backwards*" Age **9–13** yrs: **Ask**: "*Start at 50 count backwards by 3's*" Age **13** yrs & up: **Ask**: "*Start at 100 count backwards by 7's*"
Drawing	**Ask** patient to draw circle, triangle, and cross, bisect vertical and horizontal lines, and draw clock
Right/Left Orientation	Test in patients older than 6 years age: "*Show me your left hand*" and "*Show me your right hand*"
Memory, Delayed Recall	**Instruct patient**: *"I need you to memorize 3 words and will ask you to repeat them in 5 minutes. The words are "**Chair**", "**Candle**", "**Dog**" "Repeat them now to see if you have them."*

4. BEHAVIOUR (separate domain)

TEST ITEMS	Guidelines for Scoring
Activity Level	**Abnormal**: Excessively quiet, shy, removed, hyperactive, fidgety, gets up, uncontrollable, spills, into everything
Interpersonal Interaction	**Abnormal**: Clings to parent, aloof, withdrawn, gaze avoidance, punches
Cooperation	Age-dependent
Affect	**Abnormal**: Extremely shy, pouts or clings excessively or cries a lot for no reason, angry, totally flat, gaze avoidance, hyperactive, no sustained attention

Domain scores

No deficits	0
Mild deficit that does not interfere with function	0.5
Moderate deficit that interferes with function	1
Severe deficit	2

Scores for overall neurological deficit

Outcome		Definition
Good	Normal	Score = 0 in all four domains
	Mild deficit	Score = 0.5 in one domain only
Poor	Moderate deficit	Score = 0.5 in two or three domains Score = 1 in one domain and 0.5 in one domain Score = 1 in one domain
	Severe deficit	Score = 0.5 in all four domains Score = 1 in one domain and 0.5 in two domains Score = 1 in at least two domains Score = 2 in at least one domain

* PSOM, Pediatric Stroke Outcome Measure - Neuro Exam. Children's Stroke Program, Hospital for Sick Children, Toronto, Canada. G. deVeber, D. MacGregor, R. Curtis, T. Soman, R. Ichord et al. Version October 2003, revised version November 2005.

Chapter 4

Health-related quality of life in children and youth with acquired brain injury: two years after injury

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Abstract

Objective: To determine health-related quality of life (HRQoL) in children and youth with acquired brain injury (ABI) two years post-injury and explore associated factors.

Design: Cross-sectional.

Subjects: Children and youth (n=72; aged 6–22 years) with mild to severe ABI (87% mild).

Methods: The primary outcome measures self-reported and parent-reported HRQoL were assessed with the Paediatric Quality of Life Inventory (PedsQL) and compared with age-appropriate reference values of the Dutch population. Spearman correlation coefficients (Rs) were used to explore relationships between HRQoL and sociodemographic and ABI characteristics, severity of impairments and presence of post-injury problems.

Results: Children and youth with ABI and the reference population had similar self-reported HRQoL. However, as reported by parents, children with ABI aged 6–7 years and youth aged 13–18 years had poorer HRQoL regarding psychosocial health. Children's post-injury cognitive, behavioural and social problems were moderately associated with poorer HRQoL, especially psychosocial health ($R_s \geq 0.40$). Severity nor type of injury were associated with children's HRQoL.

Conclusion: Two years post-injury, in children and youth with mild to severe ABI, reported HRQoL is similar to that in the general population, whereas parents reported less favourable outcomes. Post-injury cognitive, behavioural and social problems require ongoing attention during long-term follow-up.

INTRODUCTION

Acquired brain injury (ABI) refers to any post-neonatal damage to the brain, due to an external cause (traumatic brain injury, TBI) or an internal cause (non-traumatic brain injury, NTBI) such as a brain tumour, stroke or infections such as meningitis or encephalitis [1]. In the Netherlands, the estimated yearly incidence rates in children and youth are 585/100,000 and 190/100,000, respectively for TBI and NTBI, with about 15% of ABI classified as moderate or severe [2, 3]. The consequences of NTBI are often similar to those of TBI [4].

In children and youth, ABI may have a considerable impact on their functioning [5–7] and health-related quality of life (HRQoL) [8–11]. However, results may vary between different samples and follow-up periods after injury. Studies including mild brain injuries and early assessment time points have found good HRQoL [12]. On the long-term, Anderson et al. (2010) suggested good HRQoL in adult survivors of mild and moderate TBI, and reduced HRQoL for survivors of severe TBI [13].

In children and youth with ABI, several sociodemographic, physical and psychological factors have been identified as potentially affecting HRQoL, including: greater severity of ABI [12–16], younger age at onset [13], lower level of education [13, 16], lower socioeconomic status (SES) of the parents [14, 17], family situation (single parent family) [17] and psychosocial problems [13]. In addition, pre-injury functioning of the child [14], like poorer behavioural or academic functioning [14] or pre-existing psychosocial problems [14, 17] are assumed to be important for the perceived HRQoL after brain injury.

Long-term consequences of childhood ABI (≥1 year post-injury), particularly for children with mild injury, have received limited attention and remain poorly understood [5, 8]. Clinical perceptions of long-term outcome may be negatively skewed, with only those children with severe and persisting problems presenting for healthcare services on the long term. Thus, there is little evidence to confirm whether long-term consequences reflect permanent deficits, or whether survivors have had the opportunity to 'catch up' with their peers. Parents and professionals working with children with ABI face the problem of adequately predicting outcome, and setting appropriate priorities for intervention and follow-up [16, 18]. Data on the long-term outcome of ABI regarding perceived HRQoL, using child-reported and parent-reported measures, may add to their knowledge.

Therefore, we performed a long-term follow-up study, two years after brain injury, in a heterogeneous sample of children and youth with ABI, taking into consideration age (6–22 years), type and severity of brain injury (mild, moderate and severe ABI).

The aim of the present study was to 1) investigate their HRQoL as compared with age-appropriate reference values of the Dutch population, and 2) determine associations between HRQoL and sociodemographic, injury-related and family-related characteristics, levels of physical functioning, and cognitive, behavioural or socioemotional problems.

Based on the literature and from clinical experience, we expected a poorer HRQoL for children with a more severe ABI, more severe neurologic impairments, younger age at onset, pre-injury or post-injury cognitive, behavioural or socioemotional problems, and for children from families with a lower SES.

METHODS

Design and setting

This study was part of a larger cross-sectional two-year follow-up study on outcome of ABI in children and youth aged 6–22 years living in the south-western part of the Netherlands [2, 3]. A stratified sample was drawn from a multi-centre incidence cohort of 1,892 patients with a diagnosis of ABI, year of onset 2008 or 2009, from large tertiary care hospitals in Rotterdam (Erasmus University Medical Centre, including Sophia Children's Hospital) and The Hague (Haga Hospital, including the Juliana Children's Hospital and Medical Centre Haaglanden) [2, 19]. The sample was stratified for year of onset (2008; 2009), type of injury (TBI; NTBI), severity of injury (mild; moderate; severe) and age at onset (4–12 years; 13–20 years). Data collection took place in 2010 and 2011. Severity of TBI was based on the Glasgow Coma Scale (GCS) at time of presentation in the emergency room (mild GCS 13–15, moderate GCS 9–12, severe GCS <9) (2); severity of NTBI was classified using the modified paediatric Ranking Scale (mRS), assessed at discharge from the hospital (mild mRS 0–1, moderate mRS 2–3, severe mRS 4–5) [2, 20]. Patients were first selected by age and subsequently a search in the patient files was performed using diagnosis codes and search terms related to ABI. Diagnosis codes are derived from the International Statistical Classification of Diseases and Related Health Problems (ICD-codes). The computer-based search strategy included the following terms: minor head injury, traumatic brain injury, concussion, skull/brain trauma, neurological trauma, epilepsy, brain tumour, stroke, infections (meningitis/encephalitis), post anoxia and otherwise (non-traumatic diagnosis) [2]. Participants were excluded if they were diagnosed with trauma capitis (minor head injury without brain symptoms).

The two-year follow-up study was approved by the Medical Ethical Committee (METC) of the Erasmus University Medical Centre Rotterdam (METC-2009-440). All parents and patients, as required by law from 18 years, gave written informed consent to participate.

Participants

A representative cross sectional sample of children with ABI, two years after injury. Inclusion criteria for the follow-up study were: ability to understand and complete questionnaires in Dutch. Additional inclusion criteria for the study section on HRQoL were: completed self-reported and parent-reported PedsQL. For the study section on HRQoL we excluded six children aged ≥8 years who had an intellectual disability, since they were not capable to self-report on their HRQoL. In addition, two individuals were excluded since the study was considered to be too burdensome, e.g. due to the physical, mental or emotional effort, or in case of severe pre-injury comorbidity.

As an indicator of intellectual disability we used a severe cognitive deficit on the Paediatric Stroke Outcome Measure (PSOM) (n=1) [21, 22] and/or attending special education for children with intellectual disability (indicating that they had an IQ <70/80). There is moderate agreement between normal/abnormal PSOM subscale scores with scores on corresponding domain-matched neuropsychological measures and impaired functional academic adaptive behaviour [23].

An invitation to attend a two-year follow-up assessment was sent to 433 persons; of these, 247 potential participants responded positively. No reply was largely due to inaccuracies regarding the current addresses. Of the 247 respondents, 147 (60% response rate) consented to participate. Of the two-year follow-up sample, 70 persons and their parents completed the study part related to HRQoL. Similar to Engelen et al. [24], this sample included young children (aged 6–7 years) with only a parent proxy-report of their HRQoL (n=16), and children aged ≥8 years who self-reported their HRQoL and for whom a parent proxy-report was also available (n=54). Figure 4.1 is a flowchart showing the selection of patients. Participants (n=147) and non-participants (n=70) did not differ regarding gender, severity and type of injury, but relatively more younger children (aged 6–14 years) participated (p=0.038).

Procedure

Participants were invited two years after onset of ABI for a consecutive neurological screening by trained research assistants. Parents completed the Generic Core Scales of the Paediatric Quality of Life Inventory (PedsQL) [25, 26] prior to neurological screening. Severity of impairments was assessed with a neurologic examination based on the Paediatric Stroke Outcome Measure (PSOM) and a questionnaire was used to define pre-injury and post-injury problems: cognitive/learning problems (yes/no), behavioural problems (yes/no), and socioemotional problems (yes/no). In a subsequent home visit

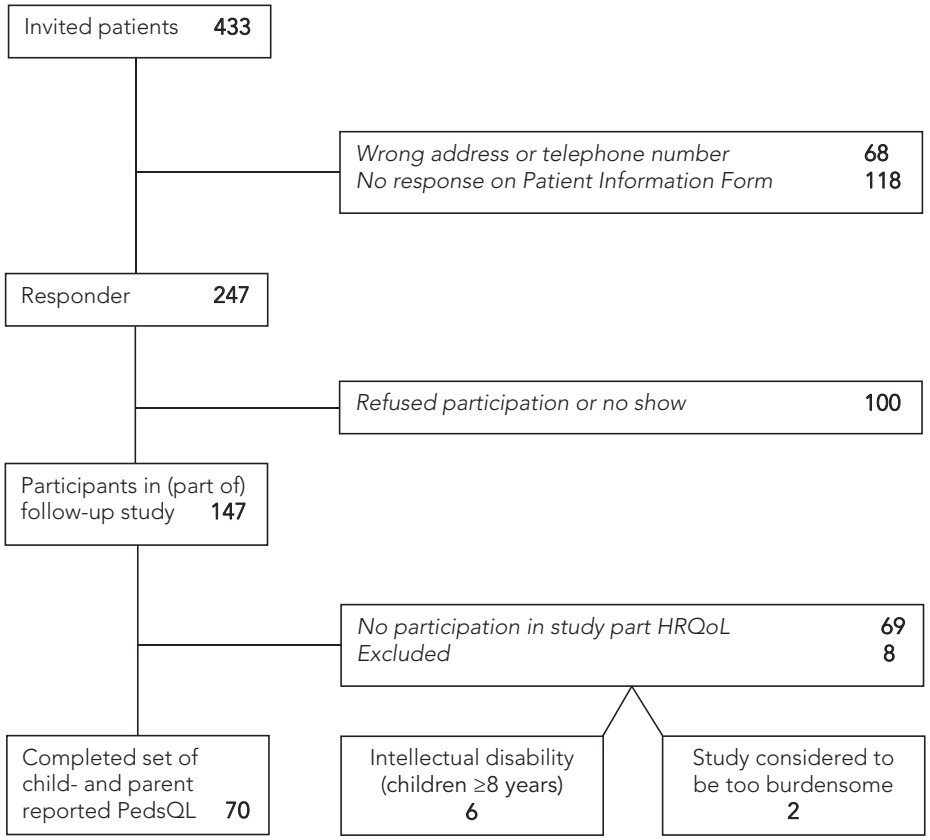

Figure 4.1 Flowchart of patient recruitment.

we assessed the children's self-reported PedsQL. Participants were informed about the results of the assessments and were referred to a physiatrist if indicated.

Measurements

Primary outcome measure

The generic core scale of the Paediatric Quality of Life Inventory (PedsQL™ 4.0 Generic Core Scales) [25, 26] was used as primary outcome measure. The PedsQL assesses HRQoL in four subdomains: physical health (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). The subdomain psychosocial health is an average of the emotional, social and school functioning scales, and the total score is an average of the scores on all four generic core scales. Items address problems in functioning scored on a 5-point Likert scale to indicate the difficulties with that item

(0 = never; 4 = almost always): examples of items are: 'I feel sad or blue' (emotional functioning), or 'I forget things' (school functioning). Each answer was reversed scored and rescaled on a 0–100 scale (0=100, 1=75, 2=50, 3=25 and 4=0), with higher scores indicating better HRQoL. The PedsQL covers a broad age range, including child self-reports as well as parent reports. Both measures comprise versions for the ages of 5–7, 8–12 and 13–18 years [25–27]. The PedsQL Generic Core Scale has good reliability and validity for a paediatric population with trauma, including TBI [25, 26, 28].

Associated factors

The following variables were assessed as factors possibly associated with HRQoL:
1) sociodemographic variables: the child's sex, age at onset and ethnicity; 2) injury-related variables: type and severity of injury; 3) variables regarding functioning: severity of impairments (PSOM), level of education, pre-injury and post-injury problems (cognitive, behavioural, and social problems); and 4) family-related variables: family situation (single/two-parent family) and SES of the parents. SES was coded using the highest educational level of one of the parents and categorised as high, intermediate or low SES (Table 4.1).

The Deficit Severity Score of the Paediatric Stroke Outcome Measure (PSOM-DSS) was used as an indicator of severity of impairments [22]. The PSOM contains 115 items assessing 5 spheres of functioning: i.e. right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavioural functioning. The DSS, ranging from 0 (no deficit) to 2 (severe deficit), was assigned for each of the 5 spheres. The PSOM is suitable for newborn to adult ages and is a valid and reliable outcome measure for paediatric stroke [21]. It was assumed that the PSOM is also useful for persons with other types of ABI, because it is a full neurological examination including a mental state examination; the items of the PSOM are not specific for stroke patients. The examination is adapted from standardised paediatric neurologic examination scales used in other childhood populations [22].

Statistical/data analysis

Descriptive statistics were computed for levels of total HRQoL and all subdomains.

We compared both parent-reported and child-reported HRQoL of the children with ABI with age-appropriate reference values of the Dutch population, using an independent-samples T-test. For this comparison we stratified participants by age group comparable to the reference population.

Factors possibly associated with HRQoL were explored univariately using Spearman correlation coefficients (R_s), since the factors studied were ordinal parameters. In addition to

the total PedsQL score, the potentially associated factors were correlated to all subdomains of the child and parent-reported PedsQL. Participants were not stratified into groups. Due to the relatively small number of patients in the category severe ABI, we also combined moderate and severe ABI to examine the association of severity with HRQoL.

For statistical analyses, the PSOM-DSS was divided into four categories: normal and mild deficit (good outcome), and moderate and severe deficit (poor outcome) [22].

Statistical significance was set at $\alpha \leq 0.05$. All data were analyzed using SPSS for Windows version 20.0.

RESULTS

Sample

Table 4.1 presents the characteristics of the 70 children participating in this part of the study: their mean age was 12.7 ± 5.2 (range 6–22) years; 55% (n=38) were boys. The type of injury was TBI in 79% (n=55) of the cases. Severity of ABI was mild in 87% (n=61), moderate in 3% (n=2) and severe in 10% (n=7). For these characteristics we observed no significant drop-out bias compared with the two-year follow-up sample (n=147) except for a low percentage of intellectual disability. Pre-injury social problems were indicated by 7% (n=5) of the patients, and post-injury social problems by 16% (n=11). Pre-injury cognition/learning and emotional problems were present in 10% (n=8) and 9% (n=6) respectively. Parents' SES was low in 11% (n=8) of patients, intermediate in 40% (n=28) and high in 40% (n=28).

HRQoL compared with reference

The HRQoL of the current sample was compared with age-appropriate reference values of the Dutch population. The reference dataset consisted of 478 healthy children with a mean age of 11.5 ± 3.0 (range 6–18) years; 46% were boys; divided into three age groups: 6–7 years (with parent proxy-report), 8–12 years and 13–18 years (with child self-report) [24]. Similar to Engelen et al. [24], we used parent-proxy reported measures for children aged 6–7 years (n=16) and child self-reported measures for children aged 8–22 years (n=54) [24]. In addition, parent proxy-reports were available for 53 of the 54 participants aged ≥8 years (Table 4.2).

Table 4.2 presents the mean ± SD scores on HRQoL of the children and youth with ABI compared with age-appropriate reference values of the Dutch population; for the ABI sample, both child self-reported and parent proxy-reported outcomes are shown.

Table 4.1 Characteristics of the 70 children and youth with ABI

Characteristics	Values n (%)	Missing n (%)
Sociodemographic		
Current age (years)		0
6–7	16 (23)	
8–12	19 (27)	
13–18	22 (31)	
19–22	13 (19)	
Sex		0
Boys	38 (55)	
Girls	32 (46)	
Ethnicity		1 (1)
Dutch	53 (76)	
Other	16 (23)	
Injury		0
Severity of injury		
Mild	61 (87)	
Moderate	2 (3)	
Severe	7 (10)	
Mild severity distribution per age group		0
6–7	15 (94)	
8–12	16 (84)	
13–18	20 (91)	
19–22	10 (77)	
Type of injury		0
Traumatic brain injury	55 (79)	
Non-traumatic brain injury	15 (21)	
Meningitis	1 (1)	
Encephalitis	1 (1)	
Tumour	7 (10)	
Epilepsy/postanoxia	3 (4)	
Ischaemic stroke	2 (3)	
ADEM, MS or other demyelinating disease	1 (1)	
Functioning		
Intellectual disability	3 (4)	0
Severity of impairments (PSOM-DSS)		0
Normal	29 (41)	
Mild deficit	16 (23)	
Moderate deficit	15 (21)	
Severe deficit	10 (14)	
Post-injury problems		
Cognition/learning	21 (30)	1 (1)
Behavioural	15 (21)	2 (3)
Social	11 (16)	1 (1)
Emotional	19 (27)	3 (4)

Table 4.1 continues on next page.

Table 4.1 *Continued*

Characteristics	Values n (%)	Missing n (%)
Child's level of education		0
Elementary school for severe learning disabilities	2 (3)	
Elementary school	34 (49)	
Junior vocational	2 (3)	
Secondary general low/senior vocational	13 (19)	
Secondary general high/higher education/university	17 (24)	
At work	2 (3)	
Family		
Socioeconomic status		6 (9)
Low*	8 (11)	
Intermediate	28 (40)	
High	28 (40)	
Family situation		4 (6)
Single-parent family	22 (31)	
Two-parent family	44 (63)	

* Low (no education, elementary school, junior vocational education), intermediate (secondary general low/high education), high (higher education and/or university level education).

The average level of HRQoL in children and youth with ABI was similar to that of the reference population, according to both children (p=0.96) and parents (p=0.15). However, according to their parents, children with ABI scored significantly lower on the subdomain psychosocial health (p=0.03). Variation in subdomains was higher in the ABI group.

Some differences were seen in specific age groups. At age 6–7 years, according to their parents, children with ABI had a significantly lower total score on the PedsQL (p=0.04), which was also seen in the subdomain psychosocial health (p=0.02).

Children aged 8–12 years (and their parents), and children aged 13–18 years, reported significantly better physical health compared with the reference population.

In addition, according to their parents, youth aged 13–18 years had a significantly poorer HRQoL on the subdomain psychosocial health (p=0.04), due to a significantly poorer HRQoL on the subdomain emotional functioning (p=0.04).

Associated factors for HRQoL

Table 4.3 shows the significantly associated factors per subdomain of the child and parent-reported PedsQL.

According to parent proxy reports, the presence of cognition/learning and social problems was moderately associated ($R_s \geq -0.40$) with poorer overall HRQoL, especially for the

Table 4.2 HRQoL scores per subdomain and age group for Dutch reference population and children and youth with ABI

Age group (years)	Subdomain	n	Dutch Reference (mean ± SD)	n	ABI (child self-report)	P∞ (T-test for mean scores)	n	ABI (parent proxy-report)	P∞ (T-test for mean scores)
6–18	Total score	478	82.6±9.0	57	82.5±11.7	0.96	57	79.7±14.7	0.15
	Physical health		85.8±9.6		88.5±11.8	**0.04***		86.2±17.4	0.86
	Psychosocial health		80.9±10.2		79.2±14.4	0.39		76.1±16.3	**0.03***
	Emotional functioning		77.0±14.1		74.6±19.3	0.38		72.7±20.0	0.13
	Social functioning		87.6±12.0		86.1±18.0	0.52		83.2±17.5	0.07
	School functioning		78.1±12.9		78.2±16.2	0.99		73.2±21.9	0.11
6–7*	Total score	74	85.0±8.6				16	76.4±14.5	**0.04***
	Physical health		87.8±9.9					84.0 ±15.6	0.22
	Psychosocial health		83.6±9.6					72.0±17.8	**0.02***
	Emotional functioning		77.5±12.7					68.7±23.3	0.17
	Social functioning		87.8±11.4					76.3±21.9	0.06
	School functioning		85.4±11.9					74.9±20.0	0.07
8–12	Total score	219	82.1±8.9	19	84.2±8.8	0.32	19	87.0±11.1	**0.03***
	Physical health		84.9±9.3		89.6±10.2	**0.04***		93.1±10.8	**0.00***
	Psychosocial health		80.6±10.3		81.3±11.5	0.78		83.5±13.5	0.37
	Emotional functioning		77.1±13.7		73.7±15.1	0.31		79.6±17.5	0.45
	Social functioning		86.1±12.3		90.5±10.7	0.13		88.6±10.5	0.40
	School functioning		78.7±12.0		79.7±16.0	0.79		81.5±18.3	0.53

Table 4.2 continues on next page.

Table 4.2 *Continued*

Age group (years)	Subdomain	n	Dutch Reference (mean ± SD)	n	ABI (child self-report)	P∞ (T-test for mean scores)	n	ABI (parent proxy-report)	P∞ (T-test for mean scores)
13–18	Total score	185	82.2±9.1	22	85.5±10.4	0.12	22	75.9±15.7	0.08
	Physical health		86.0±9.8		90.9±9.1	**0.03***		81.8±21.7	0.38
	Psychosocial health		80.2±10.2		82.7±12.5	0.30		72.8±15.7	**0.04***
	Emotional functioning		76.7±15.2		79.5±19.3	0.42		69.5±19.0	**0.04***
	Social functioning		89.4±11.6		89.3±17.9	0.99		83.6±17.7	0.15
	School functioning		74.6±13.2		79.1±13.9	0.13		65.2±23.8	0.08
19–22	Total score			13	85.3±12.9		12	85.9±14.7	
	Physical health				89.7±13.8			90.9±10.6	
	Psychosocial health				82.9±13.7			83.2±18.3	
	Emotional functioning				77.7±19.3			78.3±21.0	
	Social functioning				93.111.8			90.8±18.4	
	School functioning				78.1±20.2			80.4±22.1	

* For children aged 6–7 years we used parent-proxy reported measures, in accordance with the reference dataset.
* Significant result.

Table 4.3 Associated factors per subdomain of the child and parent-reported PedsQL with significant correlation

Outcome variable PedsQL	Associated factors	Child self-report (n=70) Spearman correlation (R_s)	Parent proxy-report (n=69) Spearman correlation (R_s)
Total score	• Severity of impairments (PSOM-DSS)	-0.33 (^)	
	• Post-injury problems		
	o Cognition/learning	-0.35 (^)	*-0.46 (#)*
	o Behavioural	-0.30 (*)	-0.38 (#)
	o Social	*-0.42 (#)*	-0.36 (^)
	o Emotional	-0.28 (*)	
	• Level of education	0.26 (*)	
Physical health	• Severity of impairments (PSOM-DSS)	-0.31 (*)	
	• Post-injury problems		
	o Cognition/learning		-0.31 (*)
Psychosocial health	• Severity of impairments (PSOM-DSS)	-0.31 (^)	
	• Post-injury problems		
	o Cognition/learning	-0.34 (^)	*-0.46 (#)*
	o Behavioural	-0.34 (^)	*-0.43 (#)*
	o Social	*-0.47 (#)*	*-0.40 (#)*
	o Emotional	-0.31 (*)	
	• Pre-injury social problems	-0.25 (*)	
Emotional functioning	• Post-injury problems		
	o Cognition/learning		*-0.45 (#)*
	o Behavioural	-0.32 (^)	-0.36 (^)
	o Social		-0.25 (*)
	o Emotional	-0.35 (^)	-0.29 (*)
	• Level of education	0.27 (*)	
Social functioning	• Severity of impairments (PSOM-DSS)	-0.33 (^)	-0.25 (*)
	• Post-injury problems		
	o Cognition/learning	-0.28 (*)	-0.32 (^)
	o Behavioural		-0.31 (^)
	o Social	*-0.47 (#)*	*-0.46 (#)*
	o Emotional	-0.28 (*)	
	• Pre-injury social problems	-0.31 (^)	-0.27 (*)
	• Level of education	0.27 (*)	
	• Age at injury	0.24 (*)	
School functioning	• Post-injury problems		
	o Cognition/learning	-0.35 (^)	*-0.41 (#)*
	o Behavioural		-0.35 (^)
	o Social	-0.32 (^)	
	• SES parents		0.28 (*)

Spearman (R_s): *p<0.05; ^p<0.01; #p≤0.001.
Italic: moderately significant association.

subdomains emotional and school functioning [cognition/learning problems (R_s=-0.45 and R_s=-0.41, respectively) and social functioning (social problems (R_s=-0.46)]. Presence of behavioural problems (R_s=-0.43) was moderately associated with poorer psychosocial health. According to child self reports, the presence of social problems was moderately associated (R_s=-0.42) with poorer overall HRQoL, especially for the subdomain social functioning (R_s=-0.47).

In addition, a poor significant association ($R_s \leq$-0.40) was found with severity of impairments (PSOM-DSS), post-injury emotional problems, pre-injury social problems, lower level of education, lower age at injury and lower SES of the parents.

HRQoL was not associated with severity of injury, whether child-reported (R_s=0.001, p=1.00) or parent-reported PedsQL (R_s=0.01, p=0.93), nor with type of injury, medical history of the child, sex, ethnicity, family situation (single-parent family) or with pre-injury problems, except for pre-injury social problems.

Checking the impact of the small subgroups of persons with severe or moderate injury, also a dichotomised distribution of mild versus moderate/severe injury did not show significant correlations with outcome in HRQoL.

DISCUSSION

Two years post-injury, children and youth (aged 6–22 years) with mild to severe ABI perceived their HRQoL to be good, as measured with the PedsQL Generic Core Scales. Overall, their HRQoL was similar to a Dutch reference population of the same age. While interpreting these results, we have to bear in mind that this was a sample of children and youth with predominantly mild ABI; only a few patients were actually being treated for the consequences of ABI.

These findings are consistent with previous studies on long-term consequences showing that paediatric survivors of, especially mild ABI, reported good HRQoL [12, 13, 16, 29].

In addition, according to their parents, children and youth with ABI scored significantly lower on psychosocial health. Literature also suggests a higher incidence of psychiatric illness after childhood mild ABI, including mood and hyperactivity disorders within three years post-injury [30, 31].

These results seems to indicate better outcomes than might be predicted from studies assessing short-term consequences within the first year after ABI [10, 17, 32]. Although, at 3 months post-injury, more children with mild or moderate TBI had normal HRQoL

compared with children with severe TBI [17]. Perceived functioning after mild to severe ABI probably continues to improve beyond the first post-injury year [18]. Future longitudinal studies with a follow-up of several years are needed to further investigate this assumption.

HRQoL compared with reference

Compared to the reference population, specifically young children (6–7 years) with ABI had a significantly poorer HRQoL as reported by parents, especially regarding their psychosocial health. However, in the present sample, in the total age range the child-reported and parent-reported HRQoL was not significantly associated with age at onset, except for a poor significant association for child-reported HRQoL on the subdomain social functioning. Thus, the present results do not add to the evidence that younger age at onset is associated with poorer HRQoL [13].

Whereas children and youth themselves rated their HRQoL relatively similar irrespective of their age, it seemed that parents did rate their child's HRQoL rather low in both the youngest (aged 6–7 years) and oldest (13–18 years) age groups (Table 4.2). Although this might be a chance finding, it might also reflect different mechanisms of development at work: 1) the young child's brain is more immature and rapidly developing and, perhaps, more susceptible to the impact of mild ABI [33–35], and 2) older children may 'grow into' their deficits because in growing-up the demands of the environment increase in complexity, which is typically toward adolescence [35].

Youth aged 13–18 years had a significantly poorer psychosocial health compared with the reference population, according to their parents. When focusing on the three components of psychosocial health, this difference appears to be due to low scores on emotional functioning. This is in line with a study of Limond et al. [8], showing that, after ABI, parental ratings of problems most frequently address emotional symptoms and social behaviour, with 8–9 times as many children in the subnormal range [8].

Regarding physical health, children and youth with ABI scored significantly better than the reference population, especially in the age groups 8–12 (child and parent-reported measures) and 13–18 years (child-reported measures). Gagnon et al. [36] showed that children aged 8–16 years returned to their premorbid level of physical activities, and maintain positive perceptions of their general athletic abilities at 3 months following a mild TBI. However, the children did not feel as confident in their ability to perform their activities at 3 months post-injury compared to how they felt before injury [36]. Probably, at 2 years post-injury their confidence has further increased making them more positive about their physical health.

Associated factors for HRQoL

In contrast to our expectations, factors assumed as being critical to outcome in the early years following paediatric ABI, such as severity or type of injury (12–16) and parental SES [14, 17, 37], were not consistently identified as factors associated with HRQoL, except for a poor association between parental SES and parent-reported HRQoL of their child in school functioning.

As aspected, post-injury cognitive, behavioural and social problems after ABI were associated with poorer HRQoL, specifically for psychosocial health. This is consistent with previous reports indicating that, after ABI, parents commonly reported poor HRQoL of their child with respect to difficulties in cognitive functioning (i.e. attention, memory and processing speed) and behavioural problems (e.g. hyperactivity, conduct and peer problems) [8, 37, 38]. Therefore, we conclude that cognitive and psychosocial problems are likely to have a negative impact on day-to-day functioning of children and youth with ABI and, as a result, their experienced HRQoL [5, 17].

HRQoL was poorly associated with severity of impairments, as assessed with the PSOM. A possible explanation for this is that, besides cognitive/behavioural deficits, two of the five subscales of the PSOM are based on sensorimotor findings and another two subscales address language; all four aspects were mildly affected [23].

Limitations

Some limitations need to be addressed when interpreting the present findings. First, the generalisability of the results is probably limited by the broad-based recruitment of the cohort. Patients were identified in hospitals at the time of injury and not in a rehabilitation setting. Thus, we included a non-referred sample of children and youth with ABI that consisted of persons with predominantly mild injury who did not require further treatment.

Few patients were classified as having an intellectual disability. Results of more specific measures assessing attention, memory and executive function may serve to further characterise the specific cognitive impairments of our sample.

The relatively high percentage of non-responders may be a confounder. Non-response was probably due to a relatively high proportion of children and youth without consequences after a mild ABI who were not interested to participate. Another reason was due to having a wrong address or telephone number, because participants were invited to join the study two years after the hospital-based diagnosis. Although response bias cannot be excluded, in the present study the characteristics of the patients at hospital admission

or discharge are fairly similar to those of the larger population [3]. However, relatively more younger children participated in our follow-up study compared to those who did not participate. Since we found no strong significant association between age at onset and HRQoL this selection is not likely to have biased the results. In order to improve the response rate in future studies, an additional assessment within the first year post-injury might be considered.

Small numbers in specific subgroups regarding age and severity of injury limited stratified analysis. On the other hand, we did stratify participants by age before comparing them with the reference population.

Furthermore, the use of the PSOM should be mentioned here. Although the PSOM was adapted from standardised paediatric neurologic examination scales for use in childhood populations [22], it was initially designed to assess children and youth after stroke [21], which is a specific subcategory of ABI. However, since the PSOM assessments are based on usual paediatric neurologic examination, we assume that the PSOM is valid for use in a broader neuropaediatric population [39].

Another limitation of the study is the use of 'yes/no' binary items to indicate the presence of cognitive, behavioural or social problems. In future studies, the use of validated scales with responses on three or more levels might further improve their sensitivity to detect differences between subgroups with less or with more severe problems.

Post-injury cognitive, behavioural and social problems should receive special attention during long term follow-up, because of their negative impact on day-to-day functioning and their experienced HRQoL, to start adequate intervention. To identify more specifically which children and adolescents may benefit from these interventions further prospective studies with larger samples are required.

Conclusions

In conclusion, two years after mild to severe ABI, children and youth with predominantly mild injury experience similar HRQoL compared with the general population. According to their parents, children aged younger than 8 years seemed to be at greater risk for a poorer HRQoL. Post-injury cognitive, behavioural and social problems should receive specific attention during long-term follow-up.

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Chapter 5

Family impact of acquired brain injury in children and youth

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Abstract

Objective: To assess the parental view on the impact of pediatric traumatic brain injury (TBI) and non-traumatic brain injury (NTBI) on the family and its determinants.

Method: Follow-up study including parents of children with a hospital-based diagnosis of acquired brain injury (ABI) aged 4–20 years at onset of ABI. Parents completed the Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM), which measures Parent Health Related Quality of Life, Family Functioning, Communication and Worry. Additional assessments included the Pediatric Stroke Outcome Measure (PSOM), the Child & Family Follow-up Survey (CFFS), PedsQL General Core and Multiple Fatigue Scales and sociodemographic and disease characteristics.

Results: Parents of 108 patients, median age 13 years (range 5–22), completed the questionnaires 24–30 months after diagnosis. There were 81 patients with TBI, of whom 11 (14%) with moderate/severe TBI and 27 patients with NTBI, of whom 5 (19%) with moderate/severe NTBI. The median PedsQL FIM Total Scale was 80.4 (SD 16.1). The PedsQL FIM Total Scale and 4 out of 5 Subscale scores were statistically significantly better in the TBI group than in the NTBI group and in patients with severe NTBI than with mild/moderate NTBI. Moreover, in the total group, there were significant univariate associations between the FIM Total Scale and/or one or more Subscale scores and age, pre-injury patient health problems and the PSOM, CFFS, PedsQL General Core and Multiple Fatigue Scales. In the multivariable analysis the FIM Total Scale was significantly associated with type and severity of injury and pre-injury patient health problems.

Conclusion: Two years after onset, the parent-reported impact of ABI on the family as measured by the PedsQL FIM was considerable, especially in patients with moderate/severe NTBI.

INTRODUCTION

Acquired brain injury (ABI) refers to any damage to the brain that occurs after birth, due to a traumatic (TBI) or non-traumatic (NTBI) cause [1]. In children and youth the yearly incidence of ABI is substantial, with estimated incidence rates for the age group 0–24 years in the Netherlands being 585 per 100,000 for TBI and 190 per 100,000 for NTBI [2], similar to incidence rates reported in the international literature [3, 4]. Overall it is found that pediatric ABI may not only have a considerable impact on the functioning and quality of life of patients with TBI [5–9] or NTBI [10–12], but on family functioning [13–15]. Consequences of pediatric ABI may have negative effects on parental coping, problem-solving, and communication [13, 16, 17], reflected by increased rates of family disruption, divorce and dysfunctioning of brothers or sisters [14, 17] after ABI. Although many families eventually adapt favorably to the often increased demands of the situation after injury, clinically significant stress is found in approximately 40% of families more than 12 months after onset of pediatric TBI [3, 14, 15]. However, long-term outcome after ABI is apart from characteristics of the injury itself, also related to environmental factors, including the functioning of the family (e.g. family cohesion, resources, social support or parent educational level/socioeconomic status) [13–18]. Regarding the factors related to the extent of parent-reported family impact, injury severity, functional impairment, health problems, behavioral changes and emotional problems after ABI were found to have a significant association with family functioning [19–23].

So far, studies in ABI used various instruments to measure family impact. The available measures for family burden or impact of trauma and/or pediatric chronic health conditions include the Impact on Family Scale (IFS) [24], Parenting Stress Index Short Form (PSI/SF) [25], Family Burden of Injury [26] and The Family Impact Module (PedsQL FIM) of the Pediatric Quality of Life Inventory (PedsQL 4.0) [27]. The PedsQL FIM seems to be a useful instrument, as it was designed as a multidimensional measure of the impact of pediatric chronic health conditions, including the physical, emotional, social and cognitive functioning of parents. These domains are found to be negatively influenced after pediatric ABI in the literature [18, 19, 28, 29]. Moreover the PedsQL FIM is available in multiple languages, including Dutch [27]. The PedsQL FIM showed good psychometric properties in parents of children with complex chronic health problems [30] and was used in studies on children with Duchenne muscular dystrophy [31], a diversity of disabilities [32] and chronic pain [33]. So far, the PedsQL FIM has not been used in studies on the family impact of ABI.

The aim of the present study was therefore to determine the parent-reported impact of pediatric TBI and NTBI on families in the Netherlands, 24–30 months after diagnosis, using

the PedsQL FIM. An important intent was to be able to assess if the previous findings from US studies generalize to the Netherlands and are similar to children with NTBI. Secondary aim was to determine associations between sociodemographic characteristics (patient and family characteristics), ABI characteristics and actual functioning on the one hand, and the parent-reported family impact as measured with the PedsQL FIM on the other hand.

METHODS

Design and setting

This study on parent-reported family impact was part of a larger, multicentre, hospital-based study on the incidence of ABI in The Netherlands [3]. In that study, performed in 2010, 1892 patients aged 0–24 years, with a first hospital-based diagnosis of ABI made in 2008 or 2009, were identified by means of a review of the medical records of the emergency ward databases and the patient admission registries of 3 large hospitals in The Netherlands (Erasmus University Medical Centre in Rotterdam, Haga Hospital, The Hague and Medical Centre Haaglanden, The Hague). In a follow-up study we aimed to determine the health status and functioning of a cohort of patients aged 4–20 years at onset of injury, approximately 2 years after onset of ABI as well as the impact on the family. The study (including the follow-up) was approved by the medical ethical committee (METC) of the Erasmus University Medical Centre Rotterdam (METC-2009-440). All parents and patients, as required by law from 18 years, participating in the follow-up assessment gave written informed consent.

Participants

For the larger study patients were selected from the registries of the participating hospitals using the following clinical diagnoses: skull/brain trauma, concussion, contusion cerebri and neurological trauma comprised TBI and brain tumour, meningitis or encephalitis, stroke, ADEM (Acute Disseminated Encephalo Myelitis), MS (Multiple Sclerosis) or acute CNS (Central Nervous System) demyelinating disease and hypoxia-ischemia were labelled as NTBI. tumour, meningitis or encephalitis, stroke, ADEM (Acute Disseminated Encephalo Myelitis), MS (Multiple Sclerosis) or acute CNS (Central Nervous System) demyelinating disease and hypoxia-ischemia. Patients were excluded if they were diagnosed with trauma capitis (minor head injury without brain symptoms). Inclusion criteria for the follow-up study were: age at onset ABI 4–20 years and ability to understand and complete questionnaires in Dutch.

Of all patients participating in the larger study, the age at onset, gender, year of onset, the type of injury (TBI or NTBI) and the severity had been extracted from the medical records. The severity of TBI was determined by means of the Glasgow Coma Scale (GCS) at hospital admission. According to the GCS, the severity of TBI was considered mild if the GCS was 13–15, moderate if the GCS was 9–12 or severe if the GCS was <9 [34]. The severity of NTBI was determined at the time of discharge after the first admission to the hospital for this particular problem, and was scored by means of an adapted version of the modified pediatric Rankin Scale (mRS) [11, 35] (school performance not taken into consideration): Mild injury: no limitations (mRS score 0, 1); Moderate injury: mild motor impairments and/or mild problems with learning (mRS 2, 3); Severe injury: severe motor impairments and/or severe problems with learning (mRS 4, 5). In addition, mRS 6 was used in cases of death during admission.

To select patients for the follow-up study the total group of participants was categorized by age (4–12 or 13–20 years at onset), year of onset (2008 or 2009), type (TBI or NTBI) and severity of injury (mild-moderate-severe), yielding 24 subgroups in total. Aiming at a total number of 400 patients to be invited for follow-up with a predicted response of 50%, 18–20 patients per subgroup were selected using 'select cases, option select random sample of cases' with the statistical software program Statistical Package For Social Sciences (SPSS) [36]. This procedure yielded a selection of 433 patients. These patients and/or their parents were subsequently approached by mail to participate in the study.

Follow-up assessments

The questionnaires were in part completed at home and in part during the visit for the examination. Within 1–3 months after informed consent was given and in the week before the examination of the child in an outpatient rehabilitation clinic, parents received 4 questionnaires to be completed at home: the PedsQL FIM [27], the Child & Family Follow-up Survey (CFFS) [37], the PedsQL General Core Scale [38] and the PedsQL Multidimensional Fatigue Scale [39]. Subsequently, about 1 week later, the child was examined in an outpatient rehabilitation clinic [40]. During the visit for the examination trained assessors interviewed parents and administered the The Pediatric Stroke Outcome Measure Short Neuro Exam (PSOM-SNE) [41]. The structured interview included questions on the presence of physical and/or mental problems of the child before the ABI and/or at present (2 questions, yes/no). In Appendix 5.1 the interpretation of scores was summarized.

Parent-reported family impact

The 36-item questionnaire yields a PedsQL FIM Total Scale Score, as well as a Parent Health Related Quality of Life (HRQoL) Summary Score (the Physical, Emotional, Social, and Cognitive Functioning Subscales; 20 items), a Family Functioning Summary Score (Daily Activities and Family Relationships Subscales; 8 items), Communication Subscale score (3 items) and a Worry Subscale score (5 items. Items are reversely scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better functioning. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in a subscale were missing, the subscale score was not computed. Other strategies for handling missing values were not applied, this computation is consistent with the previous PedsQL FIM peer-reviewed publications [42].

Overall functioning and fatigue

Two other modules of the PedsQL 4.0, pertaining to the child's health status, and both available in a Dutch language version, were used:

a. The General Core Scale [19, 42], which measures physical (8 items), emotional (5), social (5) and school functioning (5). In this study parent-report versions for children 5–7, 8–12 and 13–18 years old were used.
b. The parent version of the Multidimensional Fatigue Scale [39], designed as a child self-report and parent proxy-report generic symptom-specific instrument to measure general fatigue (6 items), sleep (6) and cognitive fatigue (6) in children. Both module scores range from 0–100, with higher scores indicating better functioning.

Participation and environmental factors

The Child & Family Follow-up Survey (CFFS) [37, 43], comprising the Child and Adolescent Scale of Participation (CASP), The Child and Adolescent Factors Inventory (CAFI) and the Child and Adolescent Scale of Environment (CASE) was used.

For both the CAFI and the CASE, higher scores indicate a greater number of problems, a greater impact of problems or a combination of the two.

Neurological functioning

The PSOM-SNE was used for the neurological functioning [41]. It includes 5 areas of functioning: right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavioural. An overall Deficit Severity Score (DSS) of normal-mild-moderate-severe, as indicator of actual level of functioning is based on the

combination of these scores, with a score range of 0–10. Lower scores indicate better functioning (less negative impact).

Statistical analysis

Characteristics of patients and parents were analysed using descriptive statistics. All continuous variables were expressed as mean with SD. Comparisons of sociodemographic and injury characteristics of participants in the present follow-up study as compared to those of all invited patients were done by means of the Mann-Whitney-U test or Chi-Square-test, where appropriate.

The family impact as measured with the PedsQL FIM, the PSOM-SNE, CFFS-DLV and PedsQL Parent reported were computed for the total group and TBI and NTBI groups separately. To assess the discriminant validity of the FIM, independent t tests were conducted and Cohen's d was calculated to compare the FIM Total and Summary Scale scores of parents with a child with TBI with those of parents with a child with NTBI. The following interpretations were used for effect size values: small (<.10–.30), medium (.30–0.50), and large (>.50) [44–46]. To determine which factors were univariably associated with parent-reported family impact, the mean PedsQL FIM Total Scale Score, HRQoL and Family Functioning Summary Scales and the two Subscales Scores Communication and Worry were compared between subgroups of patients. Subgroups were made for the following variables: Characteristics before or at onset of ABI (sociodemographic: patient age at onset and gender; educational level parents [47] and single or double parent household; presence of mental and/or physical health problems in patient before ABI; injury characteristics: type, severity); functioning 2 years after onset of ABI (actual neurological functioning, presence of mental and/or physical health problems , activities and participation, fatigue, quality of life). For the independent variables, patients were divided in subgroups according to fixed categories for nominal variables or by the median score for numeric variables. Comparisons of PedsQL FIM Total and Subscale scores between the subgroups were done by means of indepent t-tests. The Bonferroni correction was applied as post hoc test to adjust for multiple comparisons: the level of significance ($p<.5$) was divided by number of tests (n=11) resulting in a threshold for statistical significance of $p<.045$.

Then, a multivariable analysis was performed, based on the results of the univariable analysis ($p<.05$ entry level) with the PedsQL FIM Total Scale as dependent variable and sociodemographic, pre-injury and injury characteristics as independent variables. The variables concerning actual functioning (CFFS, PSOM, PedsQL General Core and Fatigue) were not entered into the multivariable prediction model, as they concerned the outcome

of ABI rather than its starting point. The variables which were not significantly associated with the outcome were dropped from the model, after a stepwise check. Results were presented as regression coefficients and explained variance. The sample size of n=108 supports the number of analyses conducted. The use of different classification systems for severity in TBI and NTBI warranted the need to conduct the analyses separately in those subgroups. As this categorization yielded a relatively small number of patients in the various categories of severity, we combined severity levels to examine the impact of TBI and NTBI on parent-reported family impact. For the multivariable analyses, a p-value less than 0.05 was adopted as the criterion for statistical significance. All data were analysed using SPSS version 21.0 software [36]. Missing values were processed according to instructions of each questionnaire.

RESULTS

Participants

The flow of patients is presented in Figure 5.1. In total, there were 147 of the 433 parents who agreed to participate in the follow-up study. Of those, 108 (60%) parents filled in the PedsQL FIM. Among these 108 participants, the numbers (in percentage) of parents completing the other assessments were the Pediatric Stroke Outcome Measure (PSOM) (106, 98%), Child and Adolescent Scale of Participation (CASP) (104, 96%), Child and Adolescent Scale of Participation (CASP) (107, 99%), Child and Adolescent Scale of Environment (CASE) (103, 95%), PedsQL General Core Scale (105, 97%). Due to the accidental sending of an incomplete set of questionnaires, only 83 parents (77%) completed the PedsQL Multidimensional Fatigue Scale.

Comparisons between participants in the follow-up study (n=147) and all invited patients (n=433) showed no significant differences regarding the distribution in age groups and types of injury.

Table 5.1 shows the characteristics of the 108 included participants with ABI and their parents. Eighty-one of the 108 patients had TBI, with 19 of 81 (23%) being classified as moderate/severe. There were 27 patients with NTBI, of whom 5 (19%) were classified as moderate/severe. Regarding the presence of mental and/or physical health problems before ABI among children, these numbers (in percentage) were 27 (26) before ABI and 39 (38) at present.

The numbers (in percentage) of parents with a low, medium and high educational level among the 100 parents who completed the question on education were 13 (13%), 40

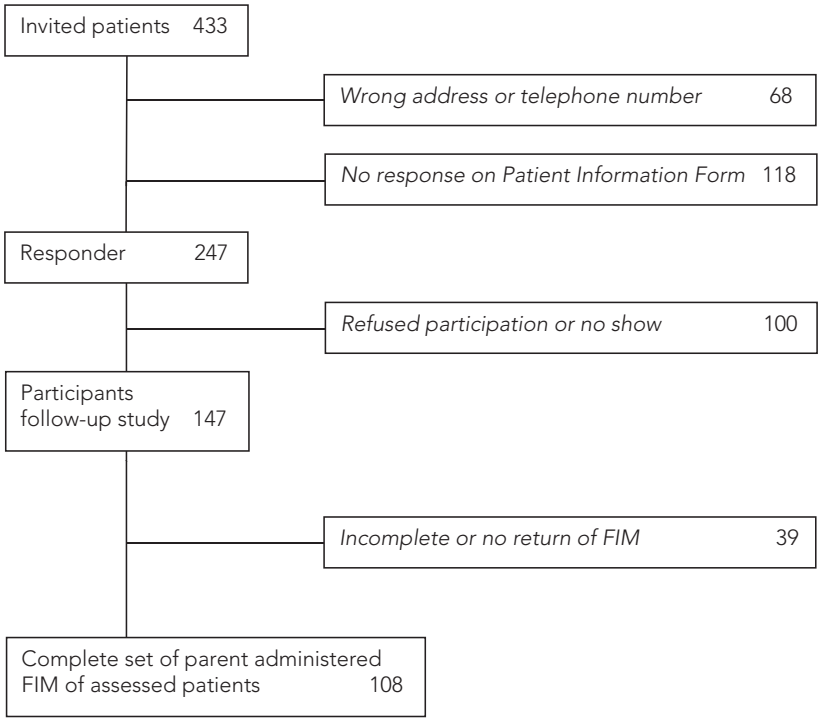

Figure 5.1 Flow chart recruitment.
FIM, Pediatric Quality of Life Family Impact Module.

(40%) and 47 (47%), respectively. Being a single parent household was reported by 31 (30%) of the parents.

Family Impact after pediatric ABI

Table 5.2 shows the results of the PedsQL FIM Total Scale Score and the Summary Scores Parent Health Related Quality of Life Score and Family Functioning in the total group and the TBI and NTBI groups.

The mean scores of the PedsQL FIM Total Scale Score and 4 out of 5 Subscale scores were significantly better in the TBI group than in the NTBI group. Moreover, the PSOM and the CASE were statistically significantly better (indicating less problems) in the TBI than in the NTBI group.

Overall, the effect sizes of the PedsQL FIM total and subscales, pertaining to differences between the TBI and NTBI groups, were large, underpinning the discriminative ability of the instrument. An exception was the Family functioning subscale, which showed a medium

Table 5.1 Characteristics of patients with acquired brain injury and their parents in a study on family impact approximately 2 years after onset

	Cohort (n=108)
Age at onset in years; median (range)	13 (5–22)
Age group ≤14 years old; number (%)	65 (60)
Sex, male; number (%)	60 (56)
Cause and severity	
Traumatic[a] Total; number (% of total ABI)	81 (75)
Mild; number (% of total TBI)	70 (86)
Moderate/severe; number (% of total TBI)	11 (14)
Non-traumatic[b] Total; number (% of total ABI)	27 (25)
Mild; number (% of total NTBI)	22 (81)
Moderate/severe; number (% of total NTBI)	5 (19)
Pre-injury patient physical or mental health problems; number (%) (n=104)	27 (26)
Actual patient physical or mental health problems; number (%) (n=103)	39 (38)
Educational level of parents; number (%) (n=100)	
Low[c]	13 (13)
Intermediate	40 (40)
High	47 (47)
Single parent household; number (%) (n=102)	31 (30)

[a] Determined by means of the Glasgow Coma Scale (GCS) at hospital admission.
[b] Determined by means of a disability scale based on the Modified Rankin Scale (mRS) at hospital discharge.
[c] Low (pre-vocational practical education or less), intermediate (pre-vocational theoretical education and upper secondary vocational education) or high (secondary education, higher education and/or university level education).
ABI, acquired brain injury; NTBI, nontraumatic brain injury; TBI, traumatic brain injury.

effect size. In general, the effect sizes of the PedsQL FIM total and subscales were in the same range or larger than those of the other instruments.

The highest possible score, meaning no problems, was reported by 12 parents (11%) for the PedsQL FIM Total Scale Score, 26 parents (24%) for the Parent Health Related Quality of Life Score and 27 parents (25%) for the Family Functioning Score. The lowest possible score, meaning maximal parent-reported family impact, was only reported once (1%), for the Subscale Worry.

Table 5.3 shows the results of the univariable analysis with the PedsQL FIM Total Scale Score, Summary and Subscale Scores as dependent variables and sociodemographic, pre-injury and injury characteristics and actual functioning as independent variables. For the independent variables, patients were divided in subgroups according to fixed categories for nominal variables or by the median score for numeric variables.

Table 5.2 Parent reported Family Impact, quality of life, fatigue, neurological functioning, and participation in 108 children with Acquired Brain Injury (ABI)

		ABI N=108	TBI N=81	NTBI N=27	p-value[a]	Cohen's d[b]
Peds QL™ FIM	Total Score (score range 0–100)	80.4 (17.9) (n=108)	83.6 (16.1) (n=81)	70.8 (19.6) (n=27)	**0.001**	**0.71**
	Parent HR QoL (score range 0–100)	81.9 (18.6) (n=107)	85.1 (17.2) (n=80)	72.6 (19.7) (n=27)	**0.002**	**0.68**
	Family functioning (score range 0–100)	78.7 (19.4) (n=107)	80.8 (18.3) (n=80)	72.3 (21.4) (n=27)	0.047	0.43
	Communication (score range 0–100)	84.6 (21.1) (n=107)	90.0 (17.1) (n=80)	69.4 (24.7) (n=27)	**<0.001**	**0.95**
	Worry (score range 0–100)	77.5 (25.3) (n=106)	83.2 (21.6) (n=79)	60.7 (28.0) (n=27)	**<0.001**	**0.90**
PSOM-SNE	Total Score (score range 0–10)	0.8 (1.2) (n=108)	0.6 (1.1) (n=81)	1.4 (1.5) (n=27)	**0.003**	**-0.61**
CFFS-DLV Parent reported	CASP Total Score (score range 0–100)	92.5 (11.3) (n=104)	93.6 (10.2) (n=77)	89.2 (9.4) (n=27)	0.077	0.37
	CAFI Total Score (score range 33.3–100)	42.3 (9.5) (n=107)	41.1 (9.2) (n=80)	45.9 (9.4) (n=27)	0.021	**-0.52**
	CASE Total Score (score range 0–100)	36.8 (5.5) (n=93)	35.8 (4.7) (n=67)	39.5 (6.5) (n=26)	**0.003**	**-0.66**
PedsQL™ Parent reported	General Core (score range 0–100)	78.2 (16.6) (n=105)	79.3 (16.6) (n=79)	75.1 (16.4) (n=26)	0.272	0.25
	Fatigue (score range 0–100)	79.7 (14.3) (n=83)	81.5 (13.7) (n=64)	73.6 (14.9) (n=19)	0.033	**0.56**

[a] P-value calculated with independent t-tests, comparing differences between the TBI and NTBI groups; **bold** values indicate statistical significance after post hoc Bonferroni correction.
[b] Cohen's d calculated through http://www.uccs.edu/;lbecker/; **bold** values indicate d > 0.50 (large effect size).
ABI, acquired brain injury; CAFI, child and adolescent factors inventory; CASE, child and adolescent scale of environment; CASP, child and adolescent scale of participation; CFFS2DLV, Child & Family Follow-up Survey2Dutch Language Version; HRQoL, health-related quality of life; NTBI, nontraumatic brain injury; PedsQL FIM, pediatric quality of life inventory family impact module; PSOM2SNE, Pediatric Stroke Outcome Measure2Short Neuro Exam; TBI, traumatic brain injury.

The FIM Communication and Worry Subscales were significantly different between younger and older patients, with lower scores in older patients. Moreover, there were significant associations between the PedsQL FIM Total Scale Score and Subscale Scores and pre-injury patient health problems, the PSOM (except for Family Functioning), CFFS and PedsQL General Core and Fatigue.

Table 5.3 Results of univariable analysis of the PedsQL™ FIM Total, Summary and Subscale Scores related to characteristics of Acquired Brain Injury (ABI) at onset (sociodemographic, pre-injury health, injury characteristics) and follow-up (actual functioning), approximately 2 years after onset of ABI*

Predictor variables	Family Impact, Total Score	Quality of Life, Summary Score	Family Functioning, Summary Score	Communication, Subscale Score	Worry, Subscale Score
Socio-demographic characteristics					
Age (at onset)					
≤14 y (n=65)[b]	82.8 (16.9)	84.4 (17.7)	79.8 (18.5)	**89.3 (17.5)**	**81.9 (22.5)**
>14 y (n=43)	76.7 (18.8)	78.2 (19.5)	77.0 (20.8)	**77.5 (24.2)**	**70.8 (27.9)**
Sex					
Male[b]	81.3 (16.9)	82.8 (17.3)	80.2 (18.2)	85.4 (20.2)	76.1 (24.6)
Female	79.3 (19.1)	80.8 (20.1)	76.7 (20.8)	83.5 (22.5)	79.2 (26.3)
Educational level parents					
Low (n=11)[b]	75.7 (16.3)	77.8 (17.0)	77.6 (20.5)	82.1 (22.0)	63.8 (28.6)
Intermediate (n=40)	78.7 (16.9)	79.3 (18.3)	77.9 (19.3)	86.1 (19.9)	78.0 (23.1)
High (n=47)	82.7 (19.9)	85.3 (19.6)	79.3 (20.6)	84.6 (22.4)	79.3 (26.8)
Single parent household					
Yes (n=31)[b]	77.0 (17.7)	78.3 (19.2)	76.5 (19.0)	85.2 (20.0)	72.7 (28.0)
No (n=71)	82.4 (17.8)	84.2 (18.0)	79.9 (19.9)	85.7 (21.2)	79.6 (24.6)
Pre-injury functioning					
Health problems					
Yes (n=27)[b]	**71.1 (21.7)**	**72.7 (23.5)**	**71.2 (22.0)**	**83.3 (26.0)**	**65.4 (25.9)**
No (n=77)	**83.4 (15.5)**	**84.9 (15.8)**	**81.3 (18.0)**	**88.6 (17.7)**	**82.0 (24.1)**

Table 5.3 *Continued*

Predictor variables	Family Impact, Total Score	Quality of Life, Summary Score	Family Functioning, Summary Score	Communication, Subscale Score	Worry, Subscale Score
Injury characteristics					
Type of injury					
TBI (n=81)[b]	83.6 (16.1)	85.1 (17.2)	80.8 (18.3)	89.7 (17.1)	83.2 (21.6)
NTBI (n=27)	70.8 (19.6)	72.6 (19.7)	72.3 (21.4)	69.4 (24.7)	60.7 (28.0)
Severity TBI					
Mild TBI (n=70)	83.8 (15.6)	85.5 (16.5)	80.6 (18.0)	89.1 (17.3)	83.3 (21.7)
Moderate/severe TBI (n=11)	82.2 (20.1)	82.0 (21.9)	82.1 (21.0)	93.2 (16.2)	82.7 (21.7)
Severity NTBI					
Mild NTBI (n=22)	75.5 (17.0)	76.7 (17.1)	78.0 (18.1)	75.0 (23.7)	65.9 (27.7)
Moderate/severe NTBI (n=5)	50.1 (18.3)	54.4 (22.0)	47.2 (16.9)	45.0 (9.5)	38.8 (18.1)
CFFS-DLV					
PSOM-SNE[a]					
Low=0 (n=42)[c]	85.1 (15.3)	86.6 (16.7)	81.7 (17.4)	89.8 (17.3)	85.9 (20.8)
High>0 (n=63)	76.5 (19.0)	78.1 (19.3)	76.1 (20.7)	80.2 (23.1)	70.5 (26.6)
CASP					
Low (≤97) (n=51)[c]	74.8 (17.8)	76.9 (18.5)	72.9 (19.7)	78.5 (22.8)	70.3 (26.4)
High (>97) (n=53)	85.2 (16.8)	86.3 (18.0)	83.6 (17.8)	90.3 (17.4)	83.9 (23.2)
CAFI[a]					
Low (≤40) (n=59)[c]	88.7 (12.2)	89.8 (12.8)	85.6 (15.8)	95.2 (11.7)	90.0 (18.1)
High (>40) (n=48)	69.9 (18.4)	72.1 (20.1)	69.5 (19.9)	70.9 (22.7)	61.3 (24.3)
CASE					
Low (≤33) (n=53)[c]	88.6 (13.1)	89.4 (13.4)	86.6 (16.0)	92.6 (16.2)	89.2 (19.6)
High (>34) (n=50)	71.1 (18.6)	73.4 (20.4)	69.8 (19.6)	75.5 (22.7)	64.0 (24.9)

Table 5.3 continues on next page.

Table 5.3 *Continued*

Predictor variables	Family Impact, Total Score	Quality of Life, Summary Score	Family Functioning, Summary Score	Communication, Subscale Score	Worry, Subscale Score
PedsQL™					
General Core[a]					
Low (≤80) (n=53)[c]	**69.9 (17.8)**	**71.8 (19.2)**	**70.2 (19.6)**	**74.9 (23.4)**	**61.8 (26.0)**
High (>80) (n=52)	**91.3 (100)**	**92.9 (9.9)**	**87.1 (15.5)**	**95.4 (10.6)**	**92.9 (12.6)**
Fatigue[a]					
Low (≤78) (n=42)[c]	**68.8 (17.5)**	**70.3 (18.7)**	**69.0 (20.1)**	**76.6 (23.4)**	**60.9 (26.9)**
High (>78) (n=41)	**93.1 (7.8)**	**95.0 (6.8)**	**88.7 (13.5)**	**97.2 (6.9)**	**94.0 (12.4)**

* All variables are expressed as mean (SD); higher score indicate better functioning, except for [a]: higher score indicates bigger problem; [b] group split in categories or [c] group split in categories by median score.
Bold values indicate significant difference between groups, tested by t-test and One way ANOVA (for Educational level parents).
TBI, Traumatic Brain Injury; NTBI, Non-Traumatic Brain Injury; PedsQL™ FIM, Pediatric Quality of Life Inventory Family Impact Module; PSOM-SNE, Pediatric Stroke Outcome Measure - Short Neuro Exam; CFFS-DLV, Child & Family Follow-up Survey-Dutch Language Version; CASP, Child and Adolescent Scale of Participation; CAFI, Child and Adolescent Factors Inventory; CASE, Child and Adolescent Scale of Environment.

Table 5.4 Results of multivariable regression analysis, with Total Score on the PedsQL™ FIM as dependent variable, approximately 2 years after onset of ABI, related to significant patient and injury characteristics at onset of ABI

	Regression coefficient B; R^2=.214	Significance level[a]	95% confidence interval
Intercept	51.7	.000	38.6–64.7
Pre-injury health problems			
No	10.2	.014	2.1–18.3
Yes	0[b]		
Type of injury			
TBI	11.5	.008	3.1–19.9
NTBI	0[b]		
Severity of injury			
Mild	10.6	.020	1.1–20.1
Moderate/severe	0[b]		

[a] p<.05.
[b] This parameter is set to zero because it is redundant.
TBI, Traumatic Brain Injury; NTBI, Non-Traumatic Brain Injury; PedsQL™ FIM, Pediatric Quality of Life Inventory Family Impact Module.

Table 5.4 shows the results of the multivariable analysis. There was no indication of possible collinearity among the independent variables to be entered in the multivariable model (sociodemographics: patient age at onset and gender; educational level parents and single or double parent household; presence of health problems before ABI; injury characteristics: type, severity) (tolerance values of all variables >.2).

In the multivariable model the type of ABI (NTBI>TBI), severity (moderate/severe > mild), and the presence of health problems in patients before ABI were associated with more parent-reported family impact, according to the PedsQL FIM Total Scale Score, with the final model accounting for 21.4% of the variance. Sex (p=.929), age at onset (p=.655), single parent household (p=.356) and parents' educational level (p=.426) were not significantly associated with parent-reported family impact, in accordance with the results of univariable analysis.

DISCUSSION

In a selected group of children and youth with acquired brain injury (ABI), with relatively many children with mild traumatic brain injury (TBI) or nontraumtic brain injury (NTBI) and only few being treated for consequences, the parent-reported impact on the family as measured by the PedsQL FIM was considerable, in particular in the NTBI group.

The family impact seen in the TBI group was similar with results from the US studies, [13-17] but comparisons are hampered as different instruments were used. The PedsQL FIM Total Scale Score in the subgroup with mild NTBI in our study was comparable with similar studies in pediatric cancer (mean 68, SD 14) [30], Duchenne (mean 65, SD 18) [31] and chronic pain (mean 65, SD 20) [33] whereas after moderate/severe NTBI, an even higher parent-reported family impact was seen.

The results of the univariable analysis showed that the parent-reported family impact was associated with the children's actual level of functioning 2 years after ABI. This finding is in line with other studies demonstrating that current health problems of children were found to have an impact family functioning after ABI [22, 48].

The prediction model of family functioning after ABI using only sociodemographic, pre-injury patient characteristics and characteristics of ABI, showed that the presence of NTBI, a greater severity and the presence of pre-injury patient health problems were associated with more parent-reported family impact. These findings are largely in line with the literature [6, 7, 21, 49]. However, the association between the type of ABI on family impact has been scarcely studied, as most studies were so far done among specific diagnosis groups (either TBI or NTBI). This difference may be due to the different nature of the two types of ABI, with TBI having a transient and/or steady course in many patients, whereas the underlying conditions in NTBI may have other consequences, such as side effects of medical treatment and risk of recurrence or relapse [11, 12]. In contrast with the literature, we found 3 baseline characteristics being not significantly associated with family impact: parents educational level [13, 22], single parent household [13], and the child's sex [49]. The absence of an association in our patient group is possibly due to the relatively average level of family impact in the TBI group.

The association between severity of ABI and the PedsQL FIM was seen in NTBI bot not in TBI. Despite the observation that the impact of severity on family functioning remained in the multivariable model including the type of ABI as a separate independent variable, it could be hypothesized that severity as determined at hospital admission is a better predictor for future functioning in NTBI than in TBI. This finding underscores the need to take the differences between the two types of ABI and the classification systems for their severity, always into account when conducting research in this area.

Several limitations of our study should be noted. First, the generalizability of the results is probably limited by the small number of participants and a relatively small number of children with moderate/severe ABI and with NTBI, the latter related to the selection of the cohort. Patient recruitment was done in hospitals and not in the rehabilitation setting.

Therefore, the population of in particular patients with TBI consisted predominantly of patients with mild ABI, not requiring treatment. The results are therefore not generalizable to groups of patients with ABI who are currently treated for the consequences [6, 7, 39]. According to literature [50, 51] approximately 20% of children with mild TBI is hindered by consequences after 3 months and 10% after 12 months, respectively. Differences with other studies may be explained by these limitations.

Moreover, the relatively high number of non-responders may indicate the presence of selection bias; however, we did not systematically record the reasons for non-participation. Some of the non-response was due to wrong addresses, and is probably random. Although response bias cannot be excluded, the characteristics of the patients participating in the present follow-up study are fairly similar to those of the larger population, which was described in a previous publication [52-54]. Nevertheless, the relatively low response resulted in an overall small sample size, which may have limited the statistical power of the study. Nevertheless, the relatively low response resulted in an overall small sample size, which may have limited the statistical power of the study. In addition, in future research yielding subgroups with sufficient sample sizes, more advanced statistical analyses could be used to minimize nonresponse bias [55].

Another limitation is time since onset: 2 years after the hospital based diagnosis is a relatively long period in which many other factors may influence outcomes such as family functioning as well, and for parents it is a long period to reflect on. Concerning the assessment of neurological functioning we used the PSOM, which has only been found to be a reliable and valid measure in pediatric stroke, but not in other forms of NTBI or in TBI. However, at the time the study was designed, it was considered the best available quantitative instrument providing a standardized neurological assessment in all diagnosis groups.

Furthermore, family functioning is a complex construct with numerous interwoven determinants, many of which are likely influence the outcomes of interest in this study. Therefore, a more detailed presentation of sociodemographic characteristics, apart from the parents' educational level, such as the degree and type of economic and social support resources that were available to the family would have been preferable. Moreover, we did not record whether the father or the mother completed the questionnaire.

Finally, a limitation of the study relates to the interpretation of the magnitude of the observed PedsQL FIM scores in the group of patients with ABI. To our knowledge, there is no literature on this subject in this patient group available yet.

Despite a number of limitations, the results of our study suggest that the PedsQL FIM is a promising, multidimensional instrument to measure parent-reported family impact in

ABI. The PedsQL Measurement Model contains several modules, designed to measure various health-related quality-of-life (HRQoL) dimensions. The PedsQL HRQoL and PedsQL Fatigue have versions for child self-report and parent report for several age groups (5–7, 8–12, 13–18 years, and 19–23 years only for the HR QoL), whereas the PedsQL Family Impact Module only has one parent version, which is not age-specific. The Subscales Communication and Worries are additional to other specific family impact measures [26, 27]. Future studies are needed to define the Minimal Clinically Important Difference (MCID) of the PedsQL FIM, the difference in scores that can be interpreted as clinically meaningful, in children with TBI and NTBI.

To overcome these shortcomings, a larger scale and longitudinal study including sufficient numbers and proportions of children with mild, moderate and severe TBI and NTBI would be needed.

CONCLUSION

Two years after onset, the parent-reported impact of Acquired Brain Injury (ABI) on the family as measured by the PedsQL FIM was considerable, especially in patients with moderate/severe nontraumatic brain injury. Future studies, for example, in a cohort referred to physical rehabilitation due to consequences of ABI, are needed to learn more about parent reported family impact and associated factors. Moreover, the responsiveness of outcome measures should be established in patients who are followed in time or in whom the effectiveness of interventions is evaluated.

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Appendix 5.1 Interpretation of scores

Measure	Abbreviation	Scores	Score range	Higher score meaning
Pediatric Quality of Life Inventory Family Impact Module Parent reported	PedsQL FIM	Total Score	0–100	Better functioning
		Parent HR QoL	0–100	Better functioning
		Family functioning	0–100	Better functioning
		Communication	0–100	Better functioning
		Worry	0–100	Better functioning
Pediatric Stroke Outcome Measure – Short Neuro Exam Professional reported	PSOM-SNE	Total Score	0–10	Worse functioning
Child & Family Follow-up Survey Parent reported	CFFS	Child and Adolescent Scale of Participation (CASP) Total Score	0–100	Better functioning
		Child and Adolescent Factors Inventory (CAFI) Total Score	33.3–100	Better functioning
		Child and Adolescent Scale of Environment (CASE) Total Score	0–100	Better functioning
Pediatric Quality of Life Inventory Health-Related Quality of Life Parent reported	PedsQL HR QoL	General Core	0–100	Worse functioning
Pediatric Quality of Life Inventory Multidimensional Fatigue Scale Parent reported	PedsQL Fatigue	Multidimensional Fatigue Scale	0–100	Worse functioning

Chapter 6

Cognitive function and participation in children and youth with mild traumatic brain injury two years after injury

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Abstract

Background: 10–20% of children and youth with mild traumatic brain injury (mTBI) suffer from long-term cognitive impairments with, supposedly, a negative impact on most domains of functioning.

Objectives: To describe cognitive functioning and participation in children and youth two-years post- mTBI and to determine associated risk factors.

Methods: Cross-sectional study among 73 patients (aged 6–22 years), hospital diagnosed with mTBI. Linear regression modelling was used to investigate the effect of potential predictors on cognitive functioning as measured with a neuropsychological assessment, two-years post-injury. Extent of participation was assessed using the Child and Adolescent Scale of Participation and correlation analysis was conducted to examine its association with level of cognitive functioning.

Results: 7–15% of all participants had impaired cognitive functions, especially in the domains of processing speed, inhibitory control, cognitive flexibility, visuospatial constructional ability and visuospatial memory. Lower level of education and pre-injury cognitive problems were predictive for a lower level of long-term cognitive functioning. Slower inhibition speed, impaired visuospatial and verbal working memory were associated with reduced participation.

Discussion and conclusions: Persisting cognitive problems two years after mTBI were mostly related to lower level of education and to pre-injury cognitive problems. Although participation of the patients was reported by parents to be relatively high, slower inhibition speed, impaired visuospatial and verbal working memory were associated with reduced participation.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability as it may cause a variety of long-term disorders across motor [1], communication [2], cognitive [3] and behavioural [4] domains resulting in decreased quality of life and high societal costs [5–8] . Worldwide each year, almost 10 million people are affected by TBI [8, 9]. Based on clinical variables such as duration of unconsciousness, amnesia and neurological symptoms, TBI can be categorised into mild, moderate and severe [10]. Mild TBI (mTBI) represents 80–90% of all cases and is typically caused by blunt non-penetrating head trauma. Individuals who sustain mTBI are likely to experience a full recovery within months to one year. However, 10–15% of patients may experience a complicated recovery with lowered satisfaction with life, and impaired cognitive functions.

mTBI is a highly prevalent diagnosis in children and youth with a yearly incidence rate of 100–300 (hospital treated) per 100,000 [9, 11]. In the Netherlands, the estimated yearly incidence rate is 271 per 100,000 in the age group 0–14 years and 262 per 100,000 in the group aged 15–24 years [12]. Despite these ominous figures many aspects of mTBI in children and youth remain uninvestigated [13, 14]. In the majority of children and youth with mTBI the cognitive deficits resolve over time [11, 15–18]. However, persistent long-term cognitive problems (inattention, slowing and forgetfulness) and substantial impairments are reported in 10–20% [3, 16, 19–22], particularly in complicated mTBI [11, 23, 24]. Early identification of children at risk for persistent cognitive deficits is of paramount importance as cognitive deficits may delay or even obstruct the acquisition of academic and social skills, causing long-term restrictions in activities and participation, a phenomenon known as 'growing into deficits'.

Prediction of long-term cognitive functioning after mTBI in children and youth helps to monitor vulnerable patients, and to optimise the use of scarce resources in long-term treatment planning. Therefore, the aim of the present study was threefold: i) to study cognitive functioning two-years post mTBI in young persons (aged 6–22 years); ii) to explore which determinants are associated with cognitive functioning two-years post-injury, and iii) to investigate associations between cognitive outcome and level of participation two-years post-injury.

We hypothesized that a lower socio-economic status (SES), more severe injuries [Glasgow Coma Scale (GCS) 13 or 14 versus 15] and the presence of pre-injury developmental problems will predict a lower level of cognitive functioning two-years post-injury [20, 22, 24–28]. Also, an association was expected between worse cognitive outcome and lower level of activities and participation.

METHODS

Participants

This study involved a subsample of patients with mTBI of a larger cross-sectional two-year follow-up study on the outcome of acquired brain injury (ABI) in children and youth aged 6–22 years, living in the southwestern part of the Netherlands [12]. A stratified sample was drawn from a multi-centre incidence cohort of 1892 patients with a diagnosis of ABI (year of onset 2008 or 2009) from large tertiary care hospitals in Rotterdam and The Hague (the Netherlands). The sample was stratified for year of onset (2008; 2009), type of injury (traumatic; non-traumatic), severity of injury (mild; moderate; severe) and age at onset (4–12 years; 13–20 years). Criteria for traumatic brain injury were: a history of observed loss of consciousness (LOC) after a head trauma, and/or symptoms related to brain injury, and/or post-traumatic amnesia (PTA), and/or abnormalities at neurological examination, and/or acute traumatic abnormalities on scan images of the brain [29].

mTBI was defined as a GCS [30] score of 13–15 at time of presentation in the emergency room and/or a duration of PTA ≤60 min [31, 32]. Participants were excluded if they were diagnosed with trauma capitis (minor head injury without brain symptoms).

An invitation to attend a two-year follow-up assessment was sent to 433 persons with ABI (Figure 6.1). Of the 247 persons who responded, 147 consented to participate (60% response rate). Participants (n=147) and non-participants (n=100) did not differ regarding gender and type of injury, but relatively more young children (6–12 years) participated (72% vs. 61%, p=0.02). Of the two-year follow-up sample, 73 participants with mTBI completed the study part related to cognitive outcome. All participants and/or their parents gave written informed consent to participate. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Centre Rotterdam (MEC-2009-440).

Measurements

Primary outcome measures

The Neuropsychological Assessment (NPA) was performed by trained neuropsychologists in an outpatient clinic of the participating hospitals. The following four subtests of the Amsterdam Neuropsychological Tasks (ANT) were used; these tasks were developed to detect subtle cognitive dysfunction with good sensitivity: Baseline Speed (BS), Shifting attentional Set-Visual (SSV), Tracking (TR) and Pursuit (PU) [33–35]. The computerised version of the ANT was used, in which instructions are followed by a training session before the start of the actual test session. These tasks consist of two parts, one for each hand

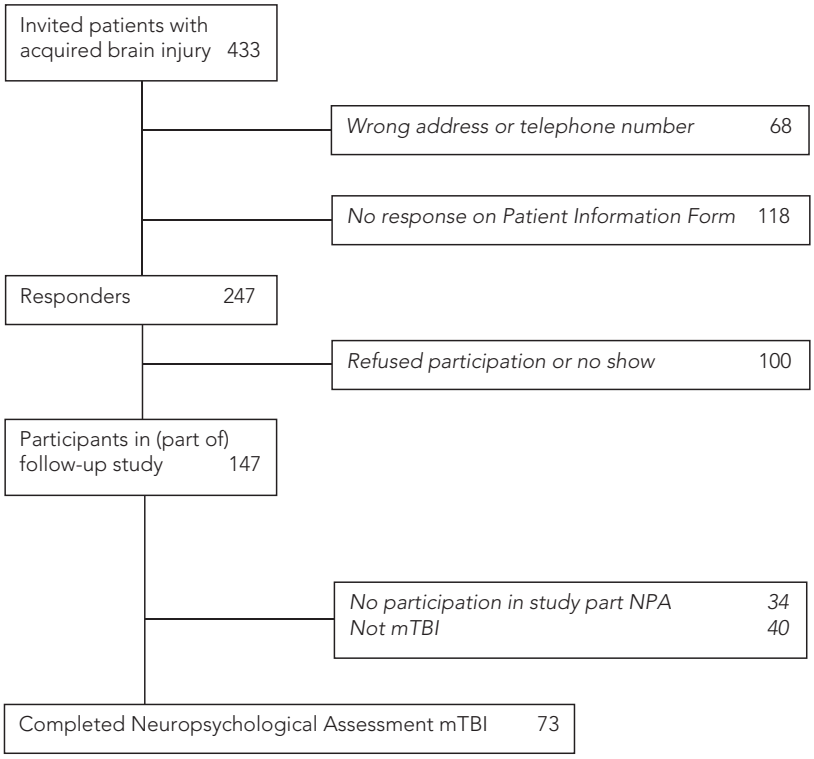

Figure 6.1 Flow chart of recruitment of participants.
NPA, Neuropsychological Assessment; mTBI, mild traumatic brain injury.

separately, in which case only data of the dominant hand were entered for the statistical analyses.

The ANT subtest BS is a reaction time task investigating information processing speed. Mean simple reaction time (ms) and stability (within-subject standard deviation; SD) calculated over the dominant hand were entered for the statistical analyses. The SSV examines the ability to inhibit prepotent responses (inhibitory control) and to adjust responses to received information (cognitive flexibility). Inhibition and flexibility speed (ms) and accuracy (percentage of errors) were included in the analyses. The TR task is a visuomotor coordination task appealing to planned and automised movements. Visuomotor accuracy (mean deviation in mm) and stability (within-subject SD) of the dominant hand were included in the analyses. The PU task is also a visuomotor coordination task, focusing on sustained attention and executive functions of nonautomised movements. Visuomotor accuracy (mean deviation in mm) and stability (within-subject SD) of the dominant hand were entered for the analyses.

The NPA was extended with the Rey Complex Figure Test and Recognition Trial (RCFT) and the Digit Span (DS). The RCFT focuses on visuospatial constructional ability and visuospatial memory (immediate and delayed recall). This test is commonly included in standard neuropsychological batteries, with a high intrarater reliability and acceptable interrater reliability [36]. A 36-point scoring system is based on accuracy and placement criteria. The DS examines short-term verbal memory and verbal working memory. This neuropsychological test is often used as a component of the Wechsler intelligence scales for children and adults [37].

Parents filled in the Child and Adolescent Scale of Participation (CASP), and were questioned about the medical history of their child and the presence of pre-injury developmental problems [13]. The CASP was recently translated into Dutch, and the reliability and validity are adequate [38]. The questionnaire measures the extent of participation and restrictions in home, school and community life situations and activities, compared to same-age peers, as reported by a parent or caregiver. The CASP consists of 20 ordinal-scaled items divided into four sections: 1) home participation (HP), 2) school participation (SP), 3) community participation (CP), and 4) home and community living activities (CLA). The items are rated on a 4-point scale (4 = age expected, 3 = somewhat limited, 2 = very limited, 1 = unable); in addition, an item can be rated as 'not applicable'. CASP summary scores (total and four subsections) are transformed to a 100-point scale by summing the scores from each applicable item, dividing this number by the maximum possible score (variable due to the number of applicable items), and multiplying this by 100. Higher scores indicate a greater extent of age-expected participation [39].

Predictive factors

The following determinants were considered as potential predictors of outcome: i) socio-demographic variables: age, sex, ethnicity (Dutch or non-native Dutch) and SES of the parents based on the educational level of the highest educated parent (low = no education or primary school; intermediate = secondary school; high = higher education), registered at follow-up; ii) injury-related variables: GCS when admitted to hospital (GCS 15; GCS 13–14), LOC (no; yes), PTA (no; yes), registered during hospital admission, and iii) pre-injury variables: level of education (elementary school for disabilities, elementary school, junior vocational, secondary vocational, secondary general high) and pre-injury developmental status of the child: motor, cognitive and social/emotional problems (no; yes), registered at follow-up.

To study a potential dose relationship between injury severity and residual cognitive impairments in mTBI, a classification of injury severity into four distinctive groups was

constructed based on the GCS, LOC and PTA. Severity score 4 was assigned to the most severe group defined by a GCS score of 13 or 14; severity score 3: GCS score 15, history of LOC *and* PTA; severity score 2: GCS score 15, history of LOC *or* PTA; severity score 1 represented mildest injury: GCS score 15, no LOC, no PTA, but symptoms related to brain injury.

Statistical/data analysis

The SPSS statistical software (version 22.0) was used to analyse the data. Prior to the major data analyses, several preprocessing steps were taken. The first step preliminary to the analyses involved checking the z-scores and SD of the continuous outcome variables for normality of the distribution. Skewness between -2 and 2 was maintained to detect outliers and meet the assumption for normality. Outliers (z-score and z-Score SD) were removed from the analyses for that particular task. CASP outcome data were checked for normality and linearity.

Descriptive analyses of outcome data were performed to describe cognitive functioning in children and youth two years after onset of injury. Given the lack of a matched control group in this study, standard z-scores were used in the ANT tasks to report the number of participants scoring below the age-appropriate norm for each outcome variable separately. The ANT programme automatically reports z-scores for each participant, using integrated norm data of thousands of healthy Dutch children and adults [33, 34]. A standard score $-1<z<1$ is regarded as normal with a positive score representing worse performance.

For RCFT the t-scores were used: t-scores ≤ 40 ($z \leq -1$) were defined as subnormal function and t-scores ≤ 30 ($z \leq -2$) were defined as impaired function. Means and SDs for DS were obtained by age level and raw scores were converted to z-scores.

The predictive value of factors for long-term cognitive functioning was estimated using linear regression analyses. First, separate univariate models were fitted for each factor on z-scores of all parameters of the subtasks (of the NPA) separately, before combining into a multiple regression model. Multivariable regression analysis with backward selection was performed on the variables that had a one-to-one association with the outcome ($p \leq 0.20$). The backward method was chosen because a preselection was already made and also to minimise type II error. GCS, LOC and PTA were included as the combined factor 'severity'. Missing values were not imputed and cases were excluded list-wise in order to confirm that the same sample was analysed in the whole model. Results are presented as standardised beta, p-values and explained variance from the multiple regression model. In addition, based on previous literature reporting that pre-injury cognitive and academic problems

are associated with worse cognitive outcome in children and youth with mTBI [18, 28] a hierarchical analysis was carried out to investigate if, next to level of education and pre-injury cognitive problems, other independent variables are able to explain the remaining variance in the subtasks of the neuropsychological assessment where level of education and pre-injury cognitive problems gave a significant association. Level of education and pre-injury cognitive problems were forced in the first block and the other independent sociodemographic factors and the factor severity of injury were added as a second block.

Descriptive analyses of CASP outcome data were performed. To explore the relationship between cognitive functioning and participation, scores on the subtasks and scores on the CASP were examined using the nonparametric test Spearman's Rank correlation. The strength of a correlation <0.30 was considered weak, 0.30 to 0.70 moderate and ≥0.70 was considered strong [40]. The level of significance was set at $p \leq 0.050$.

RESULTS

The total sample consisted of 73 participants with mTBI; of these, one participant did not complete the BS task, one did not complete the TR subtest, and three participants did not complete the PU task because they were unable to use their dominant hand sufficiently. One participant did not complete the RCFT and the DS tasks. For 11 participants no CASP outcome data were available.

Of the remaining 62 participants, two did not complete the CLA part. One child was excluded from the BS and the PU task analyses and one child from the TR task, because their scores were regarded as outliers (due to incorrect performance of the tasks).

Patient characteristics

Table 6.1 presents the characteristics of the present sample (n=73). The average age at examination was 12.59 (SD 5.09) years with boys (56.2%) and girls (43.8%) almost equally represented. A majority (58.9%) was native Dutch, 33.3% Moroccan, 25.9% Surinamese, 18.5% Turkish, and the remaining 22.3% were of varying ethnicity. The largest group had a high SES (41.1%), followed by intermediate (32.9%) and low SES (13.7%).

A GCS score of 15 was present in 50 participants; 15 participants had a GCS score of 13 or 14 (severity score 4), 18 participants had a severity score of 3 (GCS 15, history of LOC *and* PTA); 17 participants had a severity score of 2 (GCS 15, history of LOC *or* PTA); and seven participants had a severity score of 1 (GCS 15, no LOC, no PTA, but symptoms related to brain injury).

Table 6.1 Characteristics of the 73 children with mild traumatic brain injury

Characteristic	Values N (%)	Missing N
Sociodemographic		
Age (years)		0
6–22 (mean 12.59; median 12.00)	73	
Sex		0
Boys	41 (56.2)	
Girls	32 (43.8)	
Ethnicity		3
Dutch	43 (58.9)	
Non-native Dutch	27 (37.0)	
Family SES		9
Low[a]	10 (13.7)	
Intermediate[b]	24 (32.9)	
High[c]	30 (41.1)	
Injury-related		
LOC		19
Yes	33 (45.2)	
No	21 (28.8)	
PTA		20
Yes	42 (57.5)	
No	11 (15.1)	
GCS		8
15	50 (68.5)	
13 or 14	15 (20.5)	
Level of function		
Current level of education		7
Elementary school for disabilities	3 (4.1)	
Elementary school	31 (42.5)	
Junior vocational	3 (4.1)	
Secondary vocational	13 (17.8)	
Secondary general high	16 (21.9)	
Pre-injury developmental problems		
Cognition/learning	8 (11.0)	3
Social-emotional	9 (12.3)	3
Motor function	5 (6.9)	3

SES, socio-economic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale.
[a] No education or primary school; [b] Secondary school; [c] Higher education.

Cognitive functioning

Table 6.2 presents the results of the NPA. No significant differences in BS were found between our sample and norm data. However, 7.0% of the participants in our sample had z scores ≥2 for simple reaction time, indicating they were impaired with respect to

Table 6.2 Mean scores and standard deviations, and percentage of participants scoring below norm

Subtasks Cognitive function	N	Mean (SD) Raw scores	Z-score Mean (SD) T-score Mean (SD)	% subnormal Z-score ≥1 or T-score ≤40	% impaired Z-score ≥2 or T-score ≤30
Baseline speed					
Simple reaction time	71	337.85 (103.39)	-.19 (1.04)	9.9	***7.0***
Stability	71	97.44 (78.34)	-.03 (.82)	9.9	2.8
Shifting attentional Set-Visual					
Inhibition speed	73	329.45 (300.75)	.55 (1.52)	32.9	***9.6***
Inhibition accuracy	73	3.78 (6.52)	-.19 (2.51)	26.0	***13.7***
Flexibility speed	73	480.74 (365.01)	-.18 (1.64)	19.2	***6.8***
Flexibility accuracy	73	3.44 (6.75)	-.30 (2.74)	19.2	***9.6***
Tracking					
Accuracy	71	1.54 (0.78)	.22 (.75)	16.9	1.4
Stability	71	1.32 (0.81)	-.22 (.54)	1.4	0
Pursuit					
Accuracy	69	4.28 (1.60)	.17 (.64)	10.1	1.4
Stability	69	2.39 (1.15)	-.42 (.50)	2.9	0
Rey Complex Figure Test*					
Copy	72	27.94 (8.61)	50.26 (12.71)	23.6	***11.1***
Recall 1	72	15.19 (9.24)	42.42 (13.29)	43.1	***11.1***
Recall 2	72	14.69 (9.44)	42.06 (12.39)	43.1	***15.3***
Digit Span	72	13.06 (4.33)	9.63** (3.04)	23.6	***5.6***

N, number of participants; M, mean; SD, standard deviation.
Raw scores: Simple reaction time = reaction time in ms; stability = within subject standard deviation; inhibition speed = speed in ms; inhibition accuracy = percentage of errors; flexibility speed = speed in ms; flexibility accuracy = percentage of errors; tracking and pursuit accuracy = mean deviation in mm.
* T-score is used; ** Mean norm score (mean=10 in normal population).

processing speed. Subtask SSV showed no significant differences compared with norm data. However, 6.8–13.7% of the participants had z scores ≥2, indicating impairments in inhibitory control and cognitive flexibility. Especially accuracy of inhibition was impaired (13.7%). Further, the participants did not differ from the norms in the subtasks TR and PU. The mean score and SD of the RCFT did not differ from the norm population. However, 11.1–15.3% of the participants had t-scores ≤30, indicating impairments in visuospatial ability and visuospatial memory. The mean score of the DS did not differ from the norm population, with 5.6% of the participants having reduced verbal working memory.

Predictive factors

Several significant (p≤0.20) linear relationships were found between determinants and subtasks of the cognitive function parameters, and these variables were used in the multivariate models. Table 6.3 presents a summary of the determinants significantly related to the different outcomes in the multivariate regression analyses.

In the multivariate analyses: i) pre-injury cognitive problems predicted a slower and fluctuating reaction time and reduced flexibility speed; ii) lower level of education predicted reduced flexibility speed, less visuospatial constructional ability, impaired delayed recall and reduced verbal working memory; iii) younger age positively predicted inhibition speed and negatively predicted visuospatial memory; iv) female sex predicted reduced pursuit accuracy; v) being non-native Dutch predicted impaired delayed recall; vi) lower SES predicted reduced visuospatial memory; and vii) more severe injury predicted less accuracy

Table 6.3 Significant relationships between determinants and subtasks of cognitive function

Determinants	Subtasks Neuropsychological Assessment
Sociodemographic	
Age	Inhibition speed, Immediate recall (Recall 1)
Sex	Pursuit Accuracy
Ethnicity	Delayed recall (Recall 2)
SES	Immediate recall (Recall 1)
Injury-related	
Severity	Tracking accuracy
Level of function	
Level of education	Flexibility speed, Copy trial, Delayed recall (Recall 2), Digit Span
Pre-injury problems:	
Cognitive/learning	Reaction Time, Reaction Stability, Flexibility speed
Motor	-
Social-emotional	-

SES, socio-economic status.

Table 6.3A Significant relationships between determinants and six subtasks of cognitive function after controlling for level of education and pre-injury cognitive problems

Determinants	Subtasks Neuropsychological Assessment	Increase in R^2 (R^2 block 1 vs R^2 block 2)
Sociodemographic		
Sex	Reaction Time	10.3% (.078 vs .181)
Ethnicity	Delayed recall (Recall 2)	15.2% (.238 vs .390)
SES	Copy trial	10.6% (.065 vs .171)

SES, socio-economic status.

in visuomotor coordination (Table 6.3). Pre-injury motor or socio-emotional problems were not related to any neuropsychological subtask. No significant determinants were found for impaired accuracy of inhibitory control and impaired accuracy of cognitive flexibility. The results of both the univariate (and multivariate) regression analyses are presented in Tables 6.4–6.9 (Appendix).

Pre-injury cognitive problems and level of education were predictors for cognitive outcome in six of the 14 neuropsychological subtasks. The results of the hierarchical analysis, showing the additional explained variance in these subtasks after adding other independent variables, are shown in Table 6.3A.

In three neuropsychological subtasks additional effects were found: i) female sex predicted reduced reaction time; ii) being non-native Dutch predicted impaired delayed recall; iii) lower SES predicted less visuospatial constructional ability. Age and severity of injury were not found as additional factors for cognitive outcome in these six neuropsychological subtasks.

Table 6.10 Mean, standard deviations, range and percentage of participants scoring age-expected for the description of participation as measured by the CASP

CASP subsections	N	Mean	SD	Range	Age-expected	r
Total participation	62	94.09	9.90	47.50–100.00	51.6%	1.00
Home participation	62	96.91	8.86	50.00–100.00	80.6%	.59
Community participation	62	96.88	9.32	43.75–100.00	82.3%	.51
School participation	62	96.13	12.06	20.00–100.00	79.0%	.63
Community living activities	60	89.33	18.76	30.00–100.00	60.0%	.86

% age-expected = percentage of participation having the maximum score of 100.
CASP, Child and Adolescent Scale of Participation; SD, standard deviation; r, correlation coefficient between CASP Total and subsections.

Participation

Parent ratings of participation are summarized in Table 6.10. Average scores on the CASP subsections and CASP total are relatively high, and on all subsections a high percentage of participants obtained the maximum score, indicating their participation was age-expected. Lower total scores on the CASP are largely explained by lower scores on CLA. Correlations between CASP subsections and CASP total showed the strongest relationship between CLA and CASP total score (Table 6.10).

Correlations between NPA variables and CASP scores are presented in Table 6.11. Significant associations with moderate effect sizes (r=0.30–0.70) for CASP total scores were found for slower inhibition speed (r=0.30), impaired visuospatial memory (r=0.36) and impaired verbal working memory (r=0.40).

Table 6.11 Correlations between the NPA and CASP total score (95% confidence interval)

	CASP Total score		
NPA subtask	N	r	p
Baseline speed			
Simple reaction time	60	-.16	.214
Stability	60	.04	.785
Shifting Attentional Set - Visual			
Inhibition Speed	62	.30	.019*
Inhibition Accuracy	62	-.22	.086
Flexibility Speed	62	.14	.282
Flexibility Accuracy	62	-.07	.601
Tracking			
Accuracy	60	.06	.638
Stability	60	-.00	.975
Pursuit			
Accuracy	58	-.07	.583
Stability	58	-.19	.161
Rey Complex Figure Test			
Copy	62	.24	.062
Recall1	62	.28	.029*
Recall2	62	.36	.004**
Digit Span	62	.40	.001**

NPA, Neuropsychological Assessment; CASP, Child and Adolescent Scale of Participation; r, correlation coefficient; p, p-value; Spearman (R_s): *p<.05; **p<.01.

DISCUSSION

The present study shows a favourable outcome on cognitive function in a majority of children and youth aged 6–22 years two-years post-mTBI. However, 7–15% had cognitive impairments, that is impairments were found in processing speed, inhibitory control, cognitive flexibility, visuospatial constructional ability and visuospatial memory. Age, level of education and pre-injury cognitive problems were associated with long-term cognitive functioning. No significant associated factors were found for impaired accuracy of inhibitory control and impaired accuracy of cognitive flexibility. Pre-injury motor and socio-emotional problems were not associated with cognitive outcome. Slower inhibition speed, impaired visuospatial memory and impaired verbal working memory were related to lower participation levels measured with the CASP.

The aetiology of the long-term neuropsychological outcome of mTBI remains a controversial issue. Neurogenic or psychogenic explanations have been proposed [41, 42]. The present results indicate that cognitive outcome is multi-determined: age, level of education and pre-injury cognitive problems were related to more than one neuropsychological subtask. Level of education and pre-injury cognitive problems were predictors for cognitive outcome in six of the 14 subtasks. In three out of these six subtasks sex, ethnicity and SES were found as additional significant predictors. Age and severity of injury were not found as additional significant predictors in any of these subtasks. Age is known to be a predictor of outcome in TBI in young children, who are particularly vulnerable to the effects of brain injuries [43, 44]. Donders et al. [45] report an age effect in TBI on speed of information processing and high-level attention, as measured with the Trail Making Test. In a study of Crowe et al. [46], children with TBI aged 7–9 years scored worse on performance IQ and processing speed compared to children aged 10–12 years. Anderson et al. [47] established a long-term effect of mTBI in verbal fluency and story recall (verbal memory) in young children (3–7 years), but no long-term effect on intellectual ability, receptive language and spatial memory. However, in our sample the age effect is not unequivocal as older age predicted slower inhibition speed (SVV), and younger age predicted impaired visuospatial memory in immediate recall (RFCT). A lower level of education was predictive of less flexibility speed in adjusting responses to received information, less visuospatial ability, reduced visuospatial memory, and reduced verbal working memory. Pre-injury cognitive problems predicted slower and fluctuating reaction times (processing speed) and also less flexibility speed in adjusting responses to received information (flexibility speed). These findings are in line with Fay et al. who reported that cognitive reserve is an important moderator of outcome in mTBI in children and adolescents [42]. Stern [48] described that cognitive reserve may be based on more efficient utilisation of brain networks or on enhanced ability to recruit

alternate brain networks as needed, and that cognitive reserve is related to (amongst other things) level of education and pre-injury cognitive problems. In addition, TBI in children can exacerbate pre-injury attention and learning problems [49, 50], possibly by disrupting vulnerable brain networks. Tompkins et al. [51] concluded that the number of pre-injury problems in mTBI (psychological, physical or cognitive) was predictive of worse short-term visuomotor performance, but not of performance on speeded tasks and no long-term effects were found. This is not in line with the present study. Babikian et al. [28] showed no difference in neuropsychological tasks in children with mTBI and injured control children with no TBI at 12 months post-injury, compared to a non-injured control group; this suggests that these effects were a general injury effect or due to pre-injury factors and unlikely due to brain injury. On the other hand, they reported that the group children with mTBI performed worse on the Picture Memory Test (visual memory) and the Span Test (processing speed) compared to the injury control group with no TBI, in line with the present study, despite that different assessment tasks were used.

Finally, CASP participation scores reported by parents are age-expected in 51.6–82.3% with many (43.8–69.9%) having a maximum score, and lower CASP total scores were associated with slower inhibition speed, reduced visuospatial and verbal working memory. Slower inhibition speed and reduced visuospatial memory were moderately associated with reduced participation at home (HP). Impaired verbal working memory was associated with reduced participation at home (HP) and reduced community living activities (CLA). The CLA are more complex activities for independent living such as household chores, shopping and money management, managing daily schedule, using transportation, work/study activities, and responsibilities. These activities may be challenging for children and youth with impaired verbal working memory. Lower level of activities and participation is not in line with Rivara et al. [52] who reported no reduction in participation in children sustaining mild injuries after 3, 12 or 24 months, as measured with the CASP and the Adaptive Behavior Assessment System-Second Edition (ABAS-III). Other studies did find restrictions in participation after mTBI. For example, Hawley [53] showed participation problems in school in all severity TBI groups, persisting on the long term. Law et al. [54] examined participation in children with ABI using the Children's Assessment of Participation and Enjoyment (CAPE) and showed restrictions in participation, compared to healthy children, across almost all activity types in all severity groups. The measurement instrument used might explain the conflicting results compared to the better participation in the present study. For example, the CASP is known to focus on participation restrictions in broad categories, whereas the CAPE assesses the range, diversity and frequency of participation, which may reflect different aspects [6, 54]. Indeed, de Kloet et al. found no significant correlations between CASP-DLV total or subscale scores, and the diversity and

frequency aspects of the CAPE. Therefore, in our study sample, the actual participation deficits may have been masked.

Limitations and future directions

In the present study, although the relatively high percentage of non-responders may cause selection bias, the characteristics of our participants are similar to those of the original study population: as described in [12]. In the present study, the proportion of parents with high SES is relatively high (41%); this may indicate a better cognitive performance in children because SES is associated with cognitive performance and, more specifically, lower parental education is a determinant for worse cognitive performance [55, 56].

Socio-demographic factors, injury severity (complicated mTBI), level of education and pre-injury cognitive problems were associated with cognitive outcome. A few cognitive impairments were found in the absence of explored associated factors. It is unclear whether these impairments are due to the brain injury itself or due to other non-explored associated factors. In future research, we suggest to include several other factors in the prediction models. For example, the inclusion of CT-scan abnormalities may allow a more objective classification for severity, as these are reported to be predictive of increasing symptoms [20, 24]. In the present study, only 55% underwent a CT-scan. The new guidelines for patients with mTBI recently implemented in the Netherlands recommend using CT-scans in the decision-making process of mTBI treatment. This is expected to lead to more CT-scans available for inclusion in future research [57].

Finally, we performed a cross-sectional study that does not allow making inferences regarding causality. To be able to build reliable prediction models we need large numbers and prospective study designs. Therefore, there is an urgent need to develop a (inter-) national database with a core set of socio-demographics, injury-related characteristics, complication rates and long-term outcomes. This will allow identifying children at risk for unfavourable long-term outcomes who can then be followed-up over a longer period and given support when necessary.

CONCLUSION

In this sample, 7–15% of children and youth aged 6–22 years with mTBI show cognitive impairments two-years post-injury. Processing speed, inhibitory control, cognitive flexibility, visuospatial constructional ability and visuospatial memory were impaired. Level of education and pre-injury cognitive problems were associated with level of long-term

cognitive functioning. Participation of the patients was reported to be relatively high by the parents. However, we found few problems in participation in our sample. Slower inhibition speed, impaired visuospatial memory and impaired verbal working memory were associated with reduced participation.

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Table 6.4 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Baseline speed (80% confidence intervals in univariate analyses and 95% confidence intervals in multivariate analyses)

			Univar					Multivar			
			SRT			Stab		SRT		Stab	
	N	β	p	R^2	β	p	R^2	β	p	β	p
Sociodemographic											
Age	71	.02	.900	.00	.19	.111*	.04				ns
Sex[a]	71	-.14	.262	.02	.04	.759	.00				
Ethnicity[b]	68	.01	.919	.00	.07	.553	.01				
SES[c]	62	.04	.784	.00	.11	.418	.01				
Injury-related											
LOC	53	-.14	.304	.02	-.20	.152*	.04				
PTA	51	-.12	.421	.01	-.15	.298	.02				
GCS[d]	63	.09	.510	.01	.04	.766	.00				
Severity	57	.02	.865	.00	-.08	.547	.01				
Level of function											
Level of education[e]	65	-.09	.475	.01	.05	.687	.00				
Preinjury problems											
Cognitive[f]	68	.28	.022**	.08	.37	.002**	.14	.28	.022**	.37	.002**
Motor[f]	68	.01	.971	.00	-.15	.233	.02				
Socio-emotional[f]	68	.19	.112*	.04	.06	.652	.00		ns		
								R^2 .08		R^2 .14	

SRT, simple reaction time; Stab, Stability; β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes.
Baseline Speed was completed using the dominant hand. *p≤.2; **p≤.05.

Table 6.5 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Shifting attentional Set – Visual (80% confidence intervals in univariate analyses)

		Inh Speed			Inh Acc			Flex Speed			Flex Acc		
	N	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
Sociodemographic													
Age	73	.36	.002**	.13	-.12	.299	.02	.22	.057*	.05	.14	.231	.02
Sex[a]	73	.14	.235	.02	.01	.957	.00	.09	.450	.01	.12	.314	.01
Ethnicity[b]	70	.01	.906	.00	-.12	.334	.01	-.17	.169*	.03	.00	.998	.00
SES[c]	64	-.00	.985	.00	.04	.775	.00	.00	1.00	.00	.12	.329	.02
Injury-related													
LOC	54	-.29	.035**	.08	.13	.359	.02	.05	.728	.00	-.05	.734	.00
PTA	53	-.10	.461	.01	.16	.267	.02	.19	.172*	.04	-.02	.917	.00
GCS[d]	65	-.00	.978	.00	.09	.479	.01	.07	.574	.01	.20	.114*	.04
Severity	57	-.10	.464	.01	.25	.060*	.06	.12	.365	.02	.10	.481	.01
Level of function													
Level of education[e]	67	.26	.031**	.07	-.13	.298	.02	.24	.052*	.06	-.01	.938	.00
Pre-injury problems													
Cognitive[f]	70	.03	.791	.00	-.07	.541	.01	-.22	.063*	.05	.03	.798	.00
Motor[f]	70	-.07	.549	.01	.12	.316	.02	-.04	.744	.00	-.13	.286	.02
Socio-emotional[f]	70	-.06	.611	.00	.04	.770	.00	-.10	.435	.01	-.14	.262	.02

InhSpeed, inhibition speed; InhAcc, inhibition accuracy; FlexSpeed, flexibility speed; FlexAcc, flexibility accuracy; β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes.
*p≤.2; **p≤.05.

Table 6.5A Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Shifting attentional Set – Visual (95% confidence intervals in multivariate analyses)

		Inh Speed		Inh Acc		Flex Speed		Flex Acc	
	N	β	p	β	p	β	p	β	p
Sociodemographic									
Age	73	.34	.005**				ns		
Sex[a]	73								
Ethnicity[b]	70						ns		
SES[c]	64								
Injury-related									
LOC	54								
PTA	53								
GCS[d]	65								
Severity	57				ns				
Level of function									
Level of education[e]	67		ns			.26	.027**		
Pre-injury problems									
Cognitive[f]	70					-.32	.007**		
Motor[f]	70								
Socio-emotional[f]	70								
		R^2 .11		R^2 .00		R^2 .16		n.a.	

InhSpeed, inhibition speed; InhAcc, inhibition accuracy; FlexSpeed, flexibility speed; FlexAcc, flexibility accuracy; β, standardized beta; p, p-value; R^2, R square; TR^2, total R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; a 1 = girl, 2 = boy; b 1 = Dutch, 2 = other; c 1 = low, 2 = intermediate, 3 = high; d 0 = GCS 15, 1 = GCS 13 or 14; e 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; f 0 = no, 1 = yes.
*p≤.2; **p≤.05.

Table 6.6 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Tracking (80% confidence intervals in univariate analyses and 95% confidence intervals in multivariate analyses)

		Univar						Multivar			
		Accuracy			Stability			Accuracy		Stability	
	N	β	p	R^2	β	p	R^2	β	p	β	p
Sociodemographic											
Age	71	-.08	.523	.01	-.17	.146*	.03				ns
Sex[a]	71	.03	.804	.00	.00	.989	.00				
Ethnicity[b]	68	-.14	.246	.02	-.00	.982	.00				
SES[c]	62	.03	.827	.00	.01	.924	.00				
Injury-related											
LOC	52	.31	.028*	.09	.09	.546	.01				
PTA	51	.21	.145*	.04	.11	.429	.01				
GCS[d]	63	.07	.584	.01	.13	.317	.02				
Severity	51	.27	.048**	.07	.19	.171*	.04	.33	.015**		
Level of function											
Level of education[e]	65	-.06	.623	.00	-.20	.111*	.04			-.30	.031**
Pre-injury problems											
Cognitive[f]	68	-.04	.733	.00	-.08	.503	.01				
Motor[f]	68	.25	.043**	.06	.22	.068*	.05				ns
Socio-emotional[f]	68	.13	.283	.02	-.02	.902	.00				
								R^2 .11		R^2 .09	

β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes.
Tracking was completed using the dominant hand. *p≤.2; **p≤.05.

Table 6.7 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Pursuit (80% confidence intervals in univariate analyses and 95% confidence intervals in multivariate analyses)

		Univar						Multivar			
		Accuracy			Stability			Accuracy		Stabililty	
	N	β	p	R^2	β	p	R^2	β	p	β	p
Sociodemographic											
Age	69	.13	.276	.02	-.08	.503	.01				
Sex[a]	69	-.41	.001**	.17	-.19	.117*	.04	-.41	.001**		ns
Ethnicity[b]	66	.02	.871	.00	.07	.605	.00				
SES[c]	60	.00	.974	.00	.10	.440	.01				
Injury-related											
LOC	51	.01	.971	.00	.12	.417	.01				
PTA	50	-.09	.545	.01	-.02	.914	.00				
GCS[d]	61	.09	.494	.01	.21	.107*	.04				
Severity	69	.02	.911	.00	.16	.238	.03				
Level of function											
Level of education[e]	63	.07	.614	.00	-.16	.224	.02				
Pre-injury problems											
Cognitive[f]	66	-.01	.951	.00	.03	.843	.00				
Motor[f]	66	-.11	.366	.01	-.12	.344	.01				
Socio-emotional[f]	66	-.09	.491	.01	-.01	.948	.00				
								R^2 .17		R^2 .00	

β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes.
Pursuit was completed using the dominant hand. *p≤.2; **p≤.05.

Table 6.8 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Rey Copy Figure Test (80% confidence intervals in univariate analyses and 95% confidence intervals in multivariate analyses)

			Univar								Multiv					
			Copy			Recall 1			Recall2			copy		Recall1		Recall2
	N	β	p	R^2	β	p	R^2	β	p	R^2	β	p	β	p	β	p
Sociodemographic																
Age	72	.13	.283	.02	.37	.001**	.14	.32	.006**	.11			.45	.001**		
Sex[a]	72	-.06	.619	.00	-.00	.971	.00	.07	.585	.00						
Ethnicity[b]	69	-.08	.495	.00	-.36	.002**	.13	-.44	<.001**	.19				ns	-.42	<.001**
SES[c]	63	.25	.046**	.06	.19	.143*	.04	.25	.045**	.06		ns	.29	.021*		ns
Injury-related																
LOC	53	.14	.322	.02	.03	.811	.00	.17	.212	.03						
PTA	52	.11	.423	.01	.47	<.001**	.22	.46	.001**	.21						
GCS[d]	64	-.03	.806	.00	.15	.252	.02	-.05	.720	.00						
Severity	50	.06	.640	.00	.24	.074*	.06	.10	.472	.01						ns
Level of function																
Level of education[e]	66	.29	.020**	.08	.40	.001**	.16	.43	<.001**	.19	.28	.032		ns	.40	<.001**
Pre-injury problems																
Cognitive[f]	69	-.19	.119*	.04	-.05	.690	.00	-.00	.996	.00		ns				
Motor[f]	69	.08	.506	.00	-.12	.318	.02	-.11	.353	.01						
Socio-emotional[f]	69	-.10	.429	.01	-.10	.410	.01	-.07	.558	.01						
											R^2 .08		R^2 .28		R^2 .40	

β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes. *p≤.2; **p≤.05.

Table 6.9 Regression estimates for socio-demographic, injury-related and level of function variables as predictors of Digit Span (80% confidence intervals in univariate analyses and 95% confidence intervals in multivariate analyses)

			Univar		Multivar	
	N	β	p	R^2	β	p
Sociodemographic						
Age	72	.15	.198*	.02		ns
Sex[a]	72	.16	.175*	.03		ns
Ethnicity[b]	69	-.34	.005**	.11		ns
SES[c]	63	.21	.106*	.04		ns
Injury-related						
LOC	53	.27	.052*	.07		
PTA	52	.42	.002**	.18		
GCS[d]	64	.07	.583	.01		
Severity	50	.26	.050**	.07		ns
Level of function						
Level of education[e]	66	.30	.013**	.09	.32	.024**
Pre-injury problems						
Cognitive[f]	69	-.03	.786	.00		
Motor[f]	69	-.06	.622	.00		
Socio-emotional[f]	69	.03	.804	.00		
					R^2 .10	

β, standardized beta; p, p-value; R^2, R square; y, years; SES, socioeconomic status; LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; [a] 1 = girl, 2 = boy; [b] 1 = Dutch, 2 = other; [c] 1 = low, 2 = intermediate, 3 = high; [d] 0 = GCS 15, 1 = GCS 13 or 14; [e] 0 = low, 1 = elementary, 2 = junior vocational, 3 = medium, 4 = high; [f] 0 = no, 1 = yes. *p≤.2; **p≤.05.

Chapter 7

Activities and participation of children and adolescents after mild traumatic brain injury and the effectiveness of an early intervention (Brains Ahead!): study protocol for a cohort study with a nested randomized controlled trial

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Abstract

Background: Approximately 20% of children and adolescents who have sustained mild traumatic brain injuries may experience long-term consequences, including cognitive problems, posttraumatic stress symptoms and reduced load-bearing capacity. The underestimation and belated recognition of these long-term consequences may lead to chronic and disruptive problems, such as participation problems in school and in social relationships. The aim of this study is to examine the level of activities and participation of children and adolescents up to six months after a mild traumatic brain injury and to identify possible outcome predictors. Another aim is to investigate the effectiveness of an early psychoeducational intervention and compares the results with those obtained with usual care.

Methods/design: This paper presents the Brains Ahead! study design, a randomized controlled trial nested within a multicentre longitudinal prospective cohort study. The eligible participants include children and adolescents between 6 and 18 years who had experienced a mild traumatic brain injury within the last two weeks. The cohort study will include 500 children and adolescents with a mild traumatic brain injury and their caregivers. A subset of 140 participants and their caregivers will be included in the randomized controlled trial. Participants in the randomized controlled trial will be randomly assigned to either the psychoeducational intervention group or the usual care control group. The psychoeducational intervention involves one face-to-face contact and one phone contact with the interventionist, during which the consequences of mild traumatic brain injury and advice for coping with these consequences to prevent long-term problems will be discussed. Information will be provided both verbally and in a booklet. The primary outcome domain is activities and participation, which will be evaluated using the Child and Adolescent Scale of Participation. Participants are evaluated two weeks, three months and six months after the mild traumatic brain injury.

Discussion: The results of this study will provide insight into which children with mild traumatic brain injury are at risk for long-term participation problems and may benefit from an psychoeducational intervention.

Trial registration: Netherlands Trial Register identifier NTR5153. Registered on 17 Apr 2015.

BACKGROUND

The incidence of traumatic brain injury (TBI) in children between 0 and 18 years is 280–1,373/100,000 but differs by country and region [1–8]. In the Netherlands, the annual estimated incidence of TBI among children and adolescents between 0 and 24 years is 5.86 per 1,000 [9]. Therefore, approximately 12,000–14,000 cases of TBI occur among children and adolescents aged 0 to 24 years in the Netherlands each year, most (80%) of which are Mild Traumatic Brain Injuries (MTBI) [9, 10]. Children and adolescents with moderate and severe TBI generally receive follow-up care from a neurologist or rehabilitation physician, but those with MTBI typically do not [11, 12]. Notably, however, between 6 and 43% of children and adolescents with MTBI continue to experience symptoms 6 months after the injury and beyond [13–16]. MTBI in children and adolescents may lead to physical, cognitive, emotional and behavioural problems [17–19]. Several studies suggest that the post-concussive symptoms and cognitive deficits resulting from an MTBI resolve over time, but there is also evidence suggesting that these consequences persist in some children [20].

Previous studies of children who had experienced acquired brain injury (ABI) indicate that these children can also be at risk of participation limitations [21]. However, these studies often include heterogeneous groups, making it difficult to identify the participation problems accompanying MTBI more specifically [21–24]. In addition to clarifying the long-term outcomes on the level of activities and participation, more research is needed on the predictors of outcome. The predictors of activity and participation outcomes following a childhood MTBI remain unclear [25–29]. Studies on overall outcome after a childhood MTBI suggest that both injury-related (e.g., Glasgow Coma Scale score, loss of consciousness, post-traumatic amnesia) and non-injury related (e.g., age at injury, socio-economic status, family functioning) factors affect outcome [30–34]. To determine which variables predict symptom resolution after an MTBI, well-designed, long-term studies are needed [20, 35].

Early recognition of symptoms and problems after an MTBI is crucial and enables the application of early and focused interventions [35, 36]. Long-term symptoms accompanying MTBIs, such as cognitive (e.g., attention) or behavioural symptoms, are often difficult to recognize or to associate with the MTBI [30]. Delayed recognition of these invisible symptoms, underestimation of these problems and delay of diagnosis frequently and unnecessarily lead to chronic and disruptive consequences, such as activity and participation limitations (e.g., in school and social relations) [19, 37, 38]. Several studies indicate that early education, reassurance and even early cognitive behavioural approaches may be effective in preventing long-term problems after an ABI in both children and adults [39, 40] and, more specifically, after an MTBI [41–43].

Although the few available studies on interventions (e.g., psychoeducation) that prevent MTBI symptoms in children and adolescents have tended to report positive results, these studies are either retrospective or lacked a randomized controlled trial design [42–45]. The Brains Ahead! Study, using a randomised controlled trial and a large multicentre prospective cohort, is, to the author's knowledge, the first to examine the effect of a psychoeducational intervention on long-term activity and participation outcomes in children and adolescents who have experienced an MTBI.

The first aim of the Brains Ahead! study is to examine participation and activity levels in children and adolescents during the first six months after their MTBI and to identify outcome predictors. We expect that 20% of our study population will experience activity and participation problems during the first six months after their injury [13–16, 20, 21, 23, 22, 24, 30, 36]. Furthermore, we hypothesize that injury-related and non-injury related factors can predict outcomes [25–34].

The second aim is to investigate the effect of an early psychoeducational intervention on activities and participation. We hypothesize that, compared with usual care, our intervention will result in an increase in activities and participation during the first six months after an MTBI [39–45].

METHODS/DESIGN

Study design

The study is a multicentre prospective longitudinal cohort study with a nested single-blind randomized controlled trial (RCT). The RCT is conducted using a subset of participants from the cohort study (Figure 7.1) [46]. The protocol is described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist for clinical trials. Participants are followed during the first six months post-injury. During this period, there are three measurement points: two weeks (T0), three months (T1) and six months (T2) post-MTBI (Figure 7.2 and 7.3). The intervention begins two to four weeks post-injury and ends six months post-injury. The measurements and measurement times are the same for the cohort study and RCT participants. Measurements are performed by the researcher, who is blinded to the RCT group assignment.

Study population

Participants are included at the Emergency Department (ED) of one of the six participating university and general hospitals in the Netherlands (Erasmus University Hospital, Rotterdam;

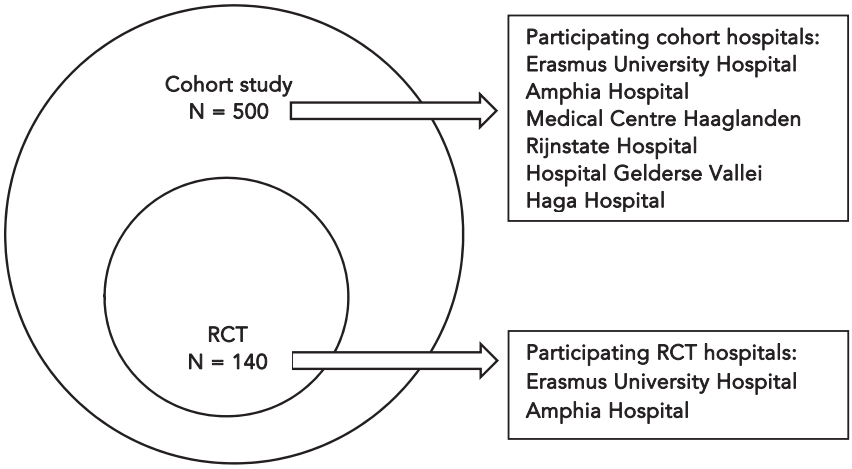

Figure 7.1 Study design.
RCT, randomised controlled trial.

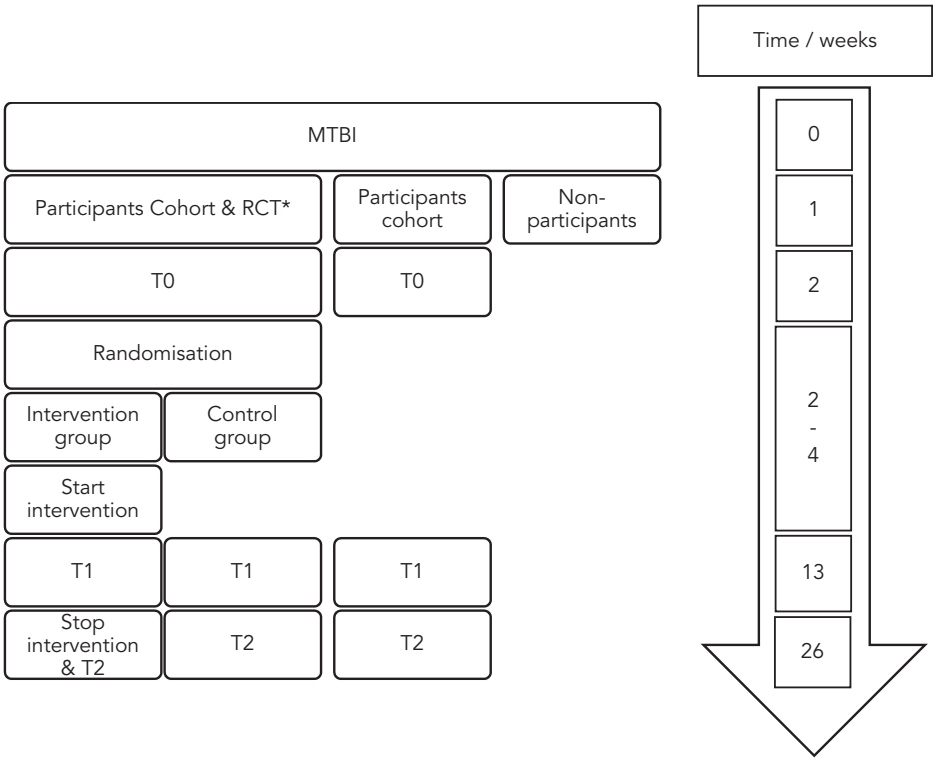

Figure 7.2 Flowchart of the study.
* The RCT is performed in intervention hospitals only. MTBI, mild traumatic brain injury.

	Enrolment	Allocation	Post-allocation	Close-out
TIMEPOINT	$-t_1$	0	t_1	T_2
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
Brains Ahead Intervention				
ASSESSMENTS:			●	●
Injury and non-injury related variables (listed in Table 7.1)		X		
Outcome variables MTBI patients (listed in Table 7.2)		X	X	X
Outcome variables caregivers (listed in Table 7.3)		X	X	X

Figure 7.3 SPIRIT checklist.
MTBI, mild traumatic brain injury.

Amphia Hospital, Breda; Medical Centre Haaglanden and Haga Hospital, The Hague; Rijnstate Hospital, Arnhem; and Hospital Gelderse Vallei, Ede). The subset of participants used for the RCT consists of participants from two of these six hospitals only (Figure 7.1). To avoid selection bias, participants recruited from both a university hospital (Erasmus University Hospital, Rotterdam) and a large general city hospital (Amphia Hospital, Breda) will participate in the RCT. Participants will be recruited between April 2015 and December 2017. The Medical Ethics Committee of Erasmus University Medical Centre, Rotterdam and all of the local committees of the participating hospitals approved the study protocol (MEC-2015-047, NL51968.078.14, v03). The study is registered in the Netherlands Trial Register (NTR5153).

Inclusion and exclusion criteria

The following Inclusion criteria must be met to participate in the study: (1) children and adolescents aged 6–18 years old and their caregivers (in this study, the caregiver is defined as a parent or guardian); (2) diagnosed with MTBI according to the criteria established by

the American Congress of Rehabilitation Medicine and the World Health Organisation Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury [47] (p. 266); and (3) informed consent provided. All caregivers and all patients aged 12 and older will provide written informed consent to participate in the cohort study, and caregivers and patients from the two RCT hospitals (Erasmus University Hospital and Amphia Hospital) will provide this for participation in the RCT as well. For children younger than 12 years, the caregiver will provide written consent. Exclusion criteria for children include having a previous objectified head trauma or having progressive neurological problems or diseases (based on patient history in the hospitals' electronic patient files), attending a day-care or school for cognitively impaired children and youth, and having insufficient knowledge of Dutch (patient or caregiver).

Patient selection and study procedures

In each of the six participating hospitals, all MTBIs are registered and communicated to the researcher. Within the first week after the MTBI, the researcher will contact the caregivers by phone to ask if they are willing to participate in the study. Subsequently, interested caregivers and patients receive written information about the study. There are two information sheets: one about the cohort study and one about the RCT. The last is only to be received by interested caregivers and patients from the two RCT hospitals. The baseline measurement (T0) is scheduled within two weeks post-injury and takes place at the participants' home only after written informed consent is obtained by the researcher. Thereafter, the subset of participants from the two hospitals that participate in the RCT are randomised and the intervention group receives the intervention. Measurements take place at three months and six months post-injury and are equal for participants in the cohort study and in the RCT (see Figure 7.2 and 7.3). The researcher is responsible for data management during the study. After the study is closed, data will be stored with the primary investigator.

Randomisation procedures

Participants who agree to be included in the RCT are randomly assigned to either the intervention or control group. Randomisation is performed after the T0 measurement which takes place within two to four weeks post-injury. It is performed by an independent person who is not involved in the recruitment, intervention or outcome measurements. The randomisation is performed using an online randomisation program that employs computerized block-randomisation, and the randomisation scheme includes stratification based on three variables: age (6–12 years or 12–18 years), gender (male or female)

and location (hospital). Caregivers are assigned to the same group as their child. After randomisation, the independent third person informs the interventionist (a professional experienced and educated in child rehabilitation after TBI) about the patients assigned to the intervention group, whereupon appointments for the intervention are scheduled.

Intervention procedures

The intervention period begins two to four weeks post-injury and extends to six months post-injury. Optimally, the intervention is offered during the early phase of recovery to prevent long-term activity and participation problems. Two scheduled sessions occur during the intervention period. The first is a face-to-face session two to four weeks after the injury; the second is a telephone follow-up session six to eight weeks after the injury. During the first 1-h face-to-face session, participants are screened for symptoms or trauma-related problems and receive individualized psychoeducation. The second session – the follow-up telephone call – will last approximately 30 minutes. Patients or caregivers can also consult the interventionist when needed. After participants have received four or more optional follow-up sessions (or fewer, based on the clinical judgement of the interventionist), the patient and caregivers are advised to contact their general practitioner for evaluation or referral.

During the intervention period, there are no restrictions on obtaining care or treatment from other professionals. However, all participants are asked to complete a patient diary every month and record any care received. Information about the sessions (e.g., date, duration, content and whether or not more extensive information on certain topics is given) and the use of additional optional follow-up sessions (e.g., date, duration, content) are recorded during the intervention period by the interventionist. Furthermore, participants, caregivers and patients 12 years and older, are individually asked to evaluate the intervention content and process at the end of the intervention.

Content of the intervention

The intervention consists of the following content:

1. *Screening of symptoms and MTBI-related problems:* A list of the ten most frequently experienced post-injury symptoms and problems was developed by our research team.

2. *Psychoeducation:* The information provided during psychoeducation includes general information about symptom occurrence, possible symptoms and practical advice for managing symptoms and developing activities for children and adolescents with MTBI and their caregivers. It also includes more extensive individualized information

about specific symptoms (e.g., headaches, dizziness and nausea, attention problems, memory problems). The general information about MTBI is provided verbally and in a written booklet. The booklet is available in three versions: a caregiver version, a version for patients aged 6–12 years and a version for patients aged 12–18 years. The individualized information is only given to participants who experience MTBI-related symptoms and is provided verbally and in writing.

3. *Follow-up:* A single follow-up is held via telephone. Depending on the needs of the patient or caregiver optional additional follow-up telephone sessions may be scheduled.

The control group receives usual care. Each hospital has a concise standard information brochure that briefly describes the possible consequences of MTBI and what to do if MTBI symptoms persist and increase. This brochure is usually given to patients in the ED.

Outcome measurements

Several injury-related and non-injury related variables are identified. These variables are presented in Table 7.1 and Figure 7.3.

Table 7.1 Injury/non-injury-related variables

Injury-related variables
Glasgow Coma Scale score (first recorded in the ambulance or ED)
Posttraumatic Amnesia duration in minutes
Loss of consciousness reported in ED
Change in mental functioning: post-acute confusion or disorientation
Other transient neurological abnormalities
CT/MRI/EEG abnormalities
Cause of MTBI
Non-injury-related variables
Location (hospital where MTBI was diagnosed)
Admission to hospital
Age of patient at injury
Gender
Educational level of patient
Pre-injury behavioural and emotional problems of the patient (measured using the CBCL)
Parental Socio Economic State (SES)
Pre-injury family function (measured using the FAD-GF)
Family situation (number of family members residing with the patient)

ED, Emergency Department; CBCL, Child Behaviour Checklist; FAD-GF, Family Assessment Device – General Functioning Scale.

Table 7.2 Outcome domains, measurement instruments and measurement moments for the patients with mild traumatic brain injury

Domain	Measurement instrument	Abbr.	Age (y)	T0	T1	T2
Activities and participation	Children's Assessment of Participation and Enjoyment	CAPE	6–18	X	X	X
	Child and Adolescent Scale of Participation – DLV*	CASP-DLV	10–18	X	X	X
Quality of Life	PedsQL** – Quality of Life Scale	PedsQL-QoL	6–18	X		X
Fatigue	PedsQL – Multidimensional Fatigue Scale	PedsQL-Fatigue	6–18	X		X
Health and behaviour	Health and Behaviour Inventory	HBI	8–18	X		X
Post-traumatic stress	Schokverwerkingslijst (Impact of Events Scale – DLV)	SVL (IES)	8–18	X		X
Sensory processing	Adolescent Adult Sensory Profile – Netherlands	AASP-NL	12–18	X		X

DLV, Dutch Language Version; PedsQL, Paediatric Quality of Life Inventory.
T0 = two weeks after MTBI; T1 = three months after MTBI; T2 = six months after MTBI.

The instruments used to measure activity and participation after an MTBI and possible outcome predictors are presented in Figure 7.3, as well as in Table 7.2 for patients and in Table 7.3 for caregivers and are described in more detail hereafter. All instruments described below are completed based on post-injury functioning, unless stated otherwise.

Given the fact that a subset of the cohort sample will receive the intervention, this might influence the outcome data in the cohort study. Therefore, if the intervention is found to be effective, the outcome data of the intervention group will be excluded from all cohort analyses (see Statistical analyses subsection below).

Primary outcome measure

The primary outcome measure, the Child and Adolescent Scale of Participation (CASP), is based on the activity and participation components of the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY).

The CASP-Dutch language version (CASP-DLV) is a 20-item questionnaire designed specifically to measure activities and participation in children who have experienced an ABI [9]. It includes a parent-report and a self-report version for children aged 10 years and older. Our primary outcome will be limited to the results of the parent-reports. The CASP-DLV items are categorized into four domains: (1) participation at home, (2) participation in the district and residence, (3) participation at school, and (4) participation at home and

Table 7.3 Outcome domains, measurement instruments and measurement moments for the caregivers

Domain	Measurement instrument	Abbr.	Age	T0	T1	T2
Activities and participation*	Child and Adolescent Scale of Participation – DLV**	CASP-DLV	All	X	X	X
Quality of Life	PedsQL*** – Quality of Life Scale	PedsQL-QoL	All	X		X
Fatigue	PedsQL – Multidimensional Fatigue Scale	PedsQL-Fatigue	All	X		X
Health and behaviour	Health and Behaviour Inventory	HBI	All	X		X
Post-traumatic stress	Schokverwerkingslijst (Impact of Events Scale – DLV)	SVL (IES)	All	X		X
Family functioning	Family Assessment Device – General Functioning	FAD-GF	All	X		X
Behaviour and emotion	Child Behaviour Checklist	CBCL	All	X		X
Sensory processing	Sensory Profile – Dutch short version	SP-NL	6–11	X		X

* Primary outcome measure; DLV, Dutch Language Version; PedsQL, Paediatric Quality of Life Inventory.
T0 = two weeks after MTBI, T1 = three months after MTBI, T2 = six months after MTBI.

in the environment. The questionnaire has been used in several international studies and has been recommended as an instrument for evaluating participation in children and adolescents after brain injury [34]. The internal consistency (Cronbach's alpha = 0.95) and test-retest reliability (intraclass correlation coefficient = 0.90) of the CASP-DLV were found to be good and to have a significant correlation with the Paediatric Quality of Life Inventory (PedsQL) (concurrent validity 0.45) [48].

Secondary outcome measures

Child and Adolescent Scale of Participation–Dutch language version self-report

The CASP-DLV self-report questionnaire for children aged 10–18 years is used as a secondary outcome measure. It evaluates participation after an MTBI from the child's perspective. The self-report version includes the same items and domains as the CASP-DLV parent-report. The self-report (or youth-report) of the original CASP is a psychometrically adequate self-report instrument for measuring activity and participation (internal consistency Cronbach's alpha = 0.87 and strong internal structure validity). It is used in conjunction with the CASP-DLV parent-version because children and adolescents may have different perceptions than their parents about their activity and participation levels

[49]. For children between the ages of 6 and 9 years, however, only the parent version is used. Information about participation from the child's perspective is obtained using the Children's Assessment of Participation and Enjoyment (CAPE).

Children's Assessment of Participation and Enjoyment

The CAPE is a 55-item questionnaire whose items correspond to 55 different activities. It measures children's participation in after-school activities [50, 51]. Five domains of participation are included: (1) diversity, (2) intensity, (3) setting/with whom the activity is typically performed, (4) usual location of the activity, and (5) the amount of pleasure the child experiences during the activity. A comparison between the CAPE and the CASP-DLV parent version showed no significant correlation, which may be because of the difference in focus of the two questionnaires: one focuses on activity restriction and the other on diversity and intensity of participation [48]. The CAPE is found to be sensitive over time when measuring functional change in children after an MTBI [27]. Furthermore, the CAPE is also a reliable and valid tool for measuring participation in recreation and leisure activities in Dutch children aged 6 -18 years with and without physical disabilities [51].

Paediatric Quality of Life inventory – Quality of Life Scale

The Paediatric Quality of Life inventory – Quality of Life Scale (PedsQL-QoL) is a 23-item questionnaire that measures health and activities, emotions, peer relations and school-related activities [52]. The questionnaire is internationally recommended for studies of children and adolescents who have experienced an ABI [25]. The psychometric properties of the Dutch PedsQL are found to be adequate, and the questionnaire is appropriate for paediatric research on health-related quality of life in the Netherlands [52].

Paediatric Quality of Life Inventory – Multidimensional Fatigue Scale

The Paediatric Quality of Life Inventory – Multidimensional Fatigue Scale (PedsQL-Fatigue) is an 18-item questionnaire that measures overall fatigue, problems regarding sleep/rest, and cognitive fatigue [53]. This questionnaire is recommended for studies of children and adolescents after an ABI [25]. The feasibility, reliability and validity of the Dutch version of the PedsQL– Multidimensional Fatigue Scale are adequate, and the scale distinguishes healthy children from children with an impaired health condition [53].

Health and Behaviour Inventory

The Health and Behaviour Inventory (HBI) is a 50-item questionnaire. It measures (1) physical, (2) emotional, (3) cognitive, and (4) behavioural symptoms. The HBI has sound psychometric properties and is able to distinguish MTBI from other injuries [25, 54].

Because a Dutch version of this inventory did not yet exist, we translated the original HBI into Dutch according to the translation guidelines [55].

Impact of Events Scale

The Dutch version of the Impact of Events Scale (IES-NL) is a 34-item questionnaire that measures possible post-traumatic stress responses [56]. The items are divided into four dimensions: (1) re-experiencing the stressor, (2) avoidance, (3) increased irritability, and (4) child-specific responses. The IES-NL has adequate reliability across various traumatic stressors and reveals a robust structure over various samples [56]. Furthermore, the questionnaire is internationally recommended for studies of children and adolescents who have experienced an ABI [25].

Family Assessment Device – General Functioning Scale

The Family Assessment Device – General Functioning Scale (FAD-GF) is a 12-item questionnaire used to measure family functioning. It has been used in previous studies on brain injuries in children [31] and is recommended for studies of pre-injury family problems and changes in family functioning associated with the traumatic brain injury [25, 57, 58]. The psychometric properties of the FAD-GF are sufficient for assessing family functioning [59]. This questionnaire is used to evaluate pre-injury family functioning at T0 and post-injury family functioning at T2.

Child Behaviour Checklist

The Child Behaviour Checklist (CBCL) is a 113-item questionnaire widely used to measure behavioural and emotional problems and skills in children [60]. This questionnaire is recommended for examining these problems in children and adolescents who have experienced an ABI and has sound psychometric properties [25, 60]. It is used to assess pre-injury behavioural and emotional problems and skills at T0 and post-injury behavioural and emotional problems and skills at T2.

Sensory Profile – Dutch Short Version and Adolescent/Adult Sensory Profile - NL

The Sensory Profile – Dutch Short Version (SP-NL) is a 38-item questionnaire. In this study, it is completed by the parents of patients between 6 and 11 years old. Patients 12 years and older complete the Adolescent/Adult Sensory Profile (AASP-NL). The questionnaires measure sensory information processing – including several sensory functions, movement abilities, and social-emotional aspects – and assess the child's activity and participation levels [61, 62]. The questionnaire adequately measures sensory information processing in children after a traumatic brain injury [63].

Sample size

Sample size calculations for the cohort study are based on the available literature about MTBI prevalence and the expected number of participants that may visit the participating hospitals. Based on an inclusion period of 2 years, the aim is to recruit a sample of 500 children and adolescents who have experienced an MTBI. Assuming a 10% dropout rate [64], our final sample should include 450 participants. Previous research shows that approximately 20% of the population will experience long-term problems [13-16, 20-24, 30, 36] after an MTBI. Therefore, approximately 90 of our participants will experience long-term problems. When conducting the regression analysis to identify the predictors of the presence of long-term problems, we should include nine determinants, based on the assumption that approximately ten participants per determinant are needed for a reliable analysis [65].

Sample size calculations for the RCT are based on the results of studies on paediatric traumatic brain injury patients' participation that relied on the parent-reports of the CASP-DLV. For the CASP-DLV, a standardized difference of 0.5 was expected [48]. With an alpha of 0.05 and a power of 0.8, a minimum of 63 children per group (control group and intervention group) is required for sufficient statistical power. Assuming a dropout rate of 10%, the aim is to recruit at least 140 children and adolescents for the RCT.

Statistical analyses

Descriptive statistics will be used to present the data on the participants, number of dropouts, losses during follow-up and the outcome measure scores. To determine the sample's representativeness and the generalizability of the results, participants will be compared to non-participants based on the inclusion and exclusion criteria. Furthermore, the baseline characteristics of participants and drops-outs and patients lost during follow-up will be compared. Comparisons will be performed using independent sample t-tests or the non-parametric equivalent.

Cohort study

To determine the results of the primary outcome measure (CASP-DLV parent-reports), descriptive statistics will be used. Continuous variables will be expressed as the means and standard deviations or as medians with interquartile ranges, depending on the distribution values. Repeated-measures analysis of variance will be used to determine the difference in activities and participation over time. If a significant difference between the measurement points ($p<0.05$) will be found, a post-hoc analysis based on Levene's test will be performed.

Linear regression analysis will be used to identify the outcome predictors of activities and participation at six months post-injury, as measured by the CASP-DLV parent reports. Within two weeks after the injury, both continuous and categorical variables (i.e., injury and non-injury related factors) are measured, as well as pre-injury family functioning (FAD-GF) and behaviour (CBCL), degree of fatigue (PedsQL-fatigue), quality of life (PedsQL-QoL), sensory processing (SP/AASP-NL), physical, cognitive, emotional and behavioural postconcussive symptoms (HBI), post-traumatic stress (Schokverwerkingslijst (Impact of Event Scale-Dutch language version)) and participation in after-school activities (CAPE). Each variable will first be examined using univariate linear regression analysis to predict activities and participation. Next, variables with values of $p<0.2$ in the univariate linear regression analysis will be included in the multivariate linear regression analysis. In the multivariate linear analysis, the significance level will be set at $p<0.05$. For more clinically relevant purposes, outcome predictors will also be determined using logistic regression analyses. If the intervention is found to be effective (see statistical analyses of RCT study, below), the data of the intervention group will be excluded from all of the cohort study analyses.

RCT

First, the baseline characteristics of the two groups will be examined using independent sample t-tests or Mann Whitney U-tests (depending on the distribution values). A chi-square test will be used to examine dichotomous variables. Next, the effectiveness of the intervention on the primary outcome measure (CASP-DLV parent-reports) will be assessed using multilevel analysis (i.e., random coefficient analysis) for both short-term (three months after injury) and long-term (six months after injury) outcomes. Time of measurement, group assignment (control or intervention group), and the interaction between time of measurement and group will be included in the multi-level regression model. The level of significance will be $p<0.05$. The random coefficient analysis will be performed with all of the participants using intention-to-treat analyses. For those with incomplete datasets, longitudinal imputation techniques will be used [66].

DISCUSSION

This paper describes the research protocol of the Brains Ahead! study. The study examines the activities and participation outcomes of children and adolescents during the first six months after experiencing an MTBI and identifies possible outcome predictors. Furthermore, this study investigates the effectiveness of an early psychoeducational intervention on activities and participation compared with the usual MTBI care received by this population. We chose for a nested design because it is preferred to gain insight

into the effect of the intervention on a short-term basis, since it might help to prevent long-term problems after MTBI in children and adolescents. In this study, a large sample is recruited for the cohort part. Taking a subset of these participants for the RCT along at the same time, enables us to investigate the effectiveness of the intervention faster than waiting on results of the cohort study first and setting up a new intervention study afterwards. We believe this is an efficient way of investigating this group of participants from an ethical perspective as well. In many studies, various types of TBI (mild, moderate, severe) are included. However, this study investigates activities and participation in children and adolescents with a mild TBI only. In a study by Ponsford et al. [42] the effectiveness of an early intervention in the form of a general information booklet was evaluated in a mild paediatric population only [42]. However, their study measured the impact of the intervention on reported symptoms, cognitive performance and psychological adjustment and not on preventing activity and participation problems. Furthermore, the sample size of their study was small (N=61) compared to the expected sample size of the present study, and the outcome was measured at three months post-injury, while this study measures the outcome at three months and six months post-injury. The strength of this study is the substantial RCT sample size extracted from a large cohort. Furthermore, the outcome instruments used in this study are largely based on the ICF-CY.

To the authors' knowledge, this is the first study to examine the effect of an early individualized psychoeducational intervention designed to prevent activity and participation problems in a relatively large group of children and adolescents following an MTBI. All of the participants in the nested RCT design receive usual care, and the intervention group receives an additional intervention. The intervention has a specific theoretical basis, and its design is based on evidence from the literature. Finally, and perhaps most importantly, the intervention is created to suit clinical practice and can be easily and directly applied in the daily practices after its effectiveness has been proven. The results of this study will provide insight into which children with MTBI are at risk for long-term participation problems and may benefit from a psychoeducational intervention.

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Chapter 8

Summary and general discussion

INTRODUCTION

Acquired brain injury (ABI) refers to damage to the brain that occurs after the neonatal period not being part of a genetic or congenital disorder [1]. It is a leading cause of morbidity in children and adolescents in developed countries [2, 3]. ABI can be divided in traumatic brain injury (TBI) and non-traumatic brain injury (nTBI). In the Netherlands, the estimated yearly incidence rates for the age group 0–24 years, are 585 per 100,000 for TBI (15,000 new cases per year) and 190 per 100,000 for nTBI (5,000 new cases per year). 10–15% of ABI in this age group is classified as moderate or severe [4, 5]. In TBI, a well-known classification of severity is the Glasgow Coma Scale (GCS) (mild GCS 13–15, moderate GCS 9–12, severe GCS <9) [6]. nTBI can be classified with the modified paediatric Ranking Scale (mRS) (mild mRS 0–1, moderate mRS 2–3, severe mRS 4–5) [7].

ABI related impairments in body functions (deficits) in children and youth have received increasing scientific attention in the past years. Motor, language, cognitive and behavioral problems are known sequelae that profoundly impact the life course of the children and families [8–10]. Even years post onset deficits and problems may impair participation and health-related quality of life (HRQoL) [11, 12]. However, research regarding long-term limitations in participation and HRQoL in patients with ABI younger than 24 years is limited and so is insight in predictors of these meaningful outcomes. Predictors of outcome can be differentiated in child-related, injury-related or socio-environmental factors. A systematic review including five studies until 2012, showed that predictors of limitations in participation were more severe ABI, problems in motor, cognitive, behavioral and sensory functions, problems in accessibility and design of the physical environment, and less acceptance and support from other people [13]. No systematic reviews have been published on prognostic factors for long-term participation after TBI in children and only two on long-term HRQoL [14, 15]. The latter reviews are limited to studies published before 2010 [14] or only focuses on mild TBI [15]. They showed that timing of outcome assessment, age, pre-injury problems (child-specific factors), severity of injury (injury-related factor) and socioeconomic status (socio-environmental factor) were predictors of long-term HRQoL.

Predictors of outcome are pivotal in planning integrated care pathways. An integrated care pathway is a multidisciplinary outline of anticipated care, placed in an appropriate timeframe, to support a patient with (sequelae of) ABI to achieve positive outcomes [16]. Identification of modifiable predictors provides the opportunity to intervene and potentially modify outcome. Therefore, finding pre-injury or post-injury mediators of outcome is of utmost importance. This thesis focused on long-term neurological outcome, participation, HRQoL and their predictors in children and youth with mild, moderate or severe ABI. In

addition, in the chapters 6 and 7 we focused more specifically on children with mild TBI.

The present chapter summarizes the main findings of this thesis and will discuss them in the broad context of existing literature. Furthermore, clinical implications and recommendations for future research are given.

MAIN FINDINGS

Chapter 2 is a systematic review summarizing 19 publications on 11 cohorts on prognostic factors of long-term (≥ 6 months) restrictions in participation and reduced quality of life (QoL) in children and adolescents with TBI. In these publications the most frequently used outcome measures for participation and HRQoL were used (respectively the Child and Adolescent Scale of Participation (CASP) and the Paediatric Quality of Life Inventory (PedsQL)) as primary outcomes.

Inconsistent evidence was found that age at injury and injury severity predict participation. Strong evidence was found that post-injury cognitive deficits predict more restrictions in participation. The variety of studied predictors of HRQoL did not allow firm conclusions. Weak evidence was found that both age at injury and pre-existing physical comorbidities did not correlate with long-term HRQoL. Inconsistent evidence was found that pre-injury mental health problems, post-injury depression, injury severity, injury-related comorbidities, socio-economic status, family functioning, health insurance and parental marital status predict long-term HRQoL. We conclude that long-term prospective studies combining multiple child-specific, injury-related, and socio-environmental factors to predict participation outcome and HRQoL at multiple endpoints are pivotal.

Chapter 3 is a cross-sectional two-year follow-up study on neurological outcome in a hospital-based cohort of children and youth (aged 6–22 years) who sustained an ABI and live in the Netherlands. Correlations with sociodemographic, injury-related, child-related and family-related characteristics were studied and in addition, associations of neurological outcome with participation restrictions were explored. A standardized pediatric neurological examination was performed according to the Paediatric Stroke Outcome Measure Short Neuro Exam (PSOM-SNE) to assess neurological function. It includes 115 items, addressing right and left sensorimotor function, language production, language comprehension, and cognitive/behavioral function. Prior to the examination, parents reported on their child's age-expected participation in four areas (Home, School, Community participation and Home/Community living activities) using the CASP, on the medical history of their child and the presence of pre-injury developmental problems.

One out of three children with ABI had a poor neurological outcome two years post onset, mostly addressing sensorimotor and cognitive deficits; nTBI and a lower educational level were negative predictors of neurological outcome. Sustaining nTBI was related to more sensorimotor and language deficits compared to TBI. Children with a lower educational level showed more cognitive deficits. Severity of brain injury, age or sociodemographic factors were not associated with neurological outcome two years post-injury. More neurological deficits and more severe deficits were associated with a restricted level of participation in all areas, especially at school.

Chapter 4 is on HRQoL two years post-injury in the same study population described in chapter 3. HRQoL was compared with age-appropriate reference values of the Dutch population and with the assessment of the caregivers. Further correlations of HRQoL with sociodemographic, child-function, injury-related, and family-related characteristics were explored. Children and parents completed the Generic Core Scales of the PedsQL that assesses HRQoL of their child in four subdomains: physical health, emotional functioning, social functioning and school functioning.

Children with mild to severe ABI perceived their HRQoL to be good two years after injury, similar to a Dutch reference population of the same age. It should be kept in mind that the large majority of the sample had a mild ABI (88%), a percentage that is in accordance to those generally reported. As judged by the parents, children with ABI aged 6–7 years and 13–18 years did score significantly lower on psychosocial health compared with the reference population specifically in emotional functioning. Those children with cognitive, behavioural and social problems post-injury had lower HRQoL scores on the long term, specifically for psychosocial health.

Chapter 5, again in the same cohort studied in chapters 3 and 4, describes the impact of ABI on the family two years post onset using the Paediatric Quality of Life Inventory Family Impact Module (PedsQL FIM) and associated factors.

The parent-reported impact on the family was considerable, in particular in the nTBI group and was associated with the children's actual level of functioning two years after ABI. nTBI, more severe nTBI and pre-injury patient health problems were associated with higher family impact.

In the chapters 6 and 7 we focused on the large subgroup of children and youth with mild TBI. In chapter 6 this is a subsample of the cohort described in chapter 3 to 5, in which we studied cognitive outcome and participation in more detail. A neuropsychological assessment was performed two years post-injury consisting of four subtests of the computerized Amsterdam Neuropsychological Tasks (ANT) extended with the Rey Complex

Figure Test and Recognition Trial and the Digit Span aimed to detect subtle cognitive dysfunction.

Cognitive impairments were present in 7–15% two years post mild TBI. Processing speed, inhibitory control, cognitive flexibility, visuospatial constructional ability and visuospatial memory were impaired. Level of education and pre-injury cognitive problems were associated with persisting cognitive problems two years after injury. Parents reported participation of the children, measured with the CASP, in 52–82% as age-expected depending on the domain of participation. Slower inhibition speed, impairments in visuospatial memory and verbal working memory were associated with restrictions in participation.

Chapter 7 presents the Brains Ahead! study design, a randomized controlled trial nested within a multicentre longitudinal prospective cohort study aimed to provide insight into which children with mild TBI are at risk for long-term participation problems. The Brains Ahead! study is a follow up of the work presented in this thesis. Children and adolescents, between 6 and 18 years old, with mild TBI within the last two weeks are included and child-specific, injury-related, and socio-environmental factors are potential predictors of outcome. Subjects are randomly assigned to either a psycho-educational intervention group or a control group receiving usual care. The psycho-educational intervention informs children and their parents on the consequences of mild TBI and advices them on coping strategies.

GENERAL CONCLUSION

Neurological deficits, restrictions in participation and reduced HRQoL can persist months and even years post-injury in children and youth with ABI. We have studied associated factors divided into child-specific, injury-related and socio-environmental factors. These studied factors (systematic review and cross-sectional cohort study) will be discussed in this paragraph and associated factors with best evidence are summarized in Table 8.1.

We showed that one out of three children with ABI had a poor neurological outcome two years post onset. Age-appropriate participation was restricted in half of the children with ABI regarding home and community living activities and psychosocial health is reduced compared to healthy peers. Psychosocial health was scored lower by parents than by children themselves which might be explained by a lack of insight of the children, or alternatively by the disability paradox referring to the discrepancy between a person's level of disability and perceived quality of life [17]. Possibly, on the long-term, children

Table 8.1 Overview of best evidence associated factors

Prognostic factor	Association
Child demographics	
Age	No association with neurological outcome, HRQoL and family impact Inconsistent association with participation
Child function factors	
Pre-injury developmental problems	Negative association*
Educational level	Positive association*
Post-injury function problems	Negative association*
Injury-related factors	
Non-traumatic brain injury (nTBI)	Negative association*
Severity	Positive association with family impact No association with neurological outcome and participation Inconsistent association with HRQoL
Socio-environmental factors	
Socio-economic status/parental education	No association with neurological outcome, participation and family impact Inconsistent association with HRQoL
Family situation (one or two parents)	No association with neurological outcome, participation and family impact. Inconsistent association with HRQoL.

* Related to all domains of outcome: neurologic outcome, participation, HRQoL and family impact.

with a disability may adapt to and be satisfied with their functioning and health. For the long-term outcome in children after ABI, contextual factors might play a role, addressing child-specific and socio-environmental factors.

Child-specific factors

Child-specific factors can be divided in 'demographic' and 'child functioning' ones. First, we did not confirm age at injury as a predictor of long-term neurological outcome, HRQoL or family impact. Only parents reported lower psychosocial health in young children with ABI (6–7 years) and in adolescents (13–18 years). Inconsistent evidence is found for age at TBI and outcome in participation. Child function factors, like pre-injury developmental problems, lower educational level and post-injury child function problems are predictors for long-term outcome. Pre-injury health problems were associated with a higher impact on the family. In addition, in line with previous research, caregivers are more likely to report family burden problems when child functioning post-injury is poorer and health care needs are unmet [10, 18]. ABI is a family affair and indeed a large number of families

used mental health counseling at some point after the injury [19, 20]. A lower educational level of the child is related to poor neurological outcome, especially cognitive deficits. The negative impact of a lower educational level or pre-injury cognitive problems possibly refer to a lower 'cognitive reserve' [21], or pre-injury problems might have been first signs of a nTBI. Impaired cognitive function at 6 months or longer post-onset is known to be a negative predictor for participation and HRQoL. Not noticing or underestimating these problems may often and unnecessarily lead to chronic and disruptive consequences, like obstruction of acquisition of academic and social skills, causing restrictions in activities and participation on the long-term [8, 22].

Injury-related factors

Overall, prognosis after nTBI is worse than after TBI. This may relate to the size or location of the brain lesion and/or to the neurotoxicity resulting from treatment like chemotherapy or cranial radiation therapy in brain tumors. In TBI poor neurological outcome varied from 21% in those with mild TBI to 40% in moderate/severe TBI. The presence of nTBI is associated with a higher impact on the family. This may be due to the different nature of the two types of ABI, with TBI having a transient and/or steady course in many patients, whereas the underlying conditions in nTBI may have other consequences, such as side effects of medical treatment and risk of recurrence or relapse. Healthcare professionals must be aware of the long-term impact of brain injury on family members and their fear for recurrence in order to support or intervene when necessary.

The severity of ABI was associated with family impact, but was not (or inconsistently) associated with neurological outcome, participation or HRQoL at two years post-injury. In the (sub)acute post-injury period, severity of injury appears to be a critical predictor for outcome in TBI [8, 21], but in long term severity of injury may become less important where type of injury (nTBI or TBI) and/or child-specific factors (child function problems) become more important. Besides this, positive compensatory development of the brain, interventions and/or modification of the environment may play a role in a better long-term outcome. Thus, children who have a poor neurological function at discharge may be able to achieve appropriate levels of age-expected participation and HRQoL.

Socio-environmental factors

No evidence or inconsistent evidence is found for socio-economic status/parent education level and family situation as predictors for neurological outcome, participation, HRQoL and family impact. In other studies higher quality of home environment and social support of

family and friends was associated with better long-term participation at school and in the community, suggesting that a better environment helps to moderate the consequences of ABI [23–26]. Function of family or environment is a complex construct with numerous interwoven determinants. A more detailed presentation of socio-environmental factors, such as the degree and type of economic and social support, is needed to investigate the influence of socio-environmental factors on long-term outcomes in children after ABI.

CLINICAL IMPLICATIONS

The present findings suggest that children and youth with pre-injury developmental problems, more severe ABI (especially nTBI), persistent cognitive impairments and poor neurological outcome on the long term need close monitoring in order to detect problems and to offer timely intervention programs. Even children with relatively good neurological outcome at discharge may suffer from serious and persisting consequences due to the immaturity of the young brain and the risk of disruption of ongoing psychosocial development. Based on clinical experience we assume that this may result in increasing gaps in functioning between brain injured children and their peers when growing up.

The absence of valid prognostic algorithms on long-term outcome after pediatric ABI requires integrated care pathways that ensure that at any moment in time adequate support is guaranteed when needed. In many western countries, like in the Netherlands, follow-up care from a child-neurologist or rehabilitation physician is offered to children and adolescents after sustaining moderate and severe ABI, but typically not after sustaining mild TBI because complete recovery is expected, usually within two to three months [27]. The Centers for Disease Control and Prevention in the United States have recently developed a guideline on the diagnosis and management of mild TBI in children based on current evidence [28]. Recommendations are made related to counseling on prognosis and assessment of cumulative risk factors, but also in this subgroup prognostic algorithms are missing. As it is not possible to identify which children with mild brain injuries at discharge will have limitations in participation or reduced HRQoL on the long-term, follow-up by a general practitioner after mild brain injury in children and youth is to be advised. In this follow-up special attention should be paid to child-function factors, like cognitive, behavioral and social function problems. If these problems are still present at three months post-injury, leading to restrictions in activities and participation, referral to specialized care by a pediatrician, neurologist or pediatric physiatrist is recommended [28, 29]. Since cognitive problems post-injury were found as strong predictor for reduced long-term participation, awareness of these hidden consequences is necessary to provide

better healthcare. Sometimes subtle cognitive (or behavioral) problems at long- term are difficult to recognize, especially when the brain injury itself is almost forgotten. Monitoring of these cognitive function problems is important during the development of the child into adulthood.

In the Netherlands, a standard of care and integrated care pathways were developed for stroke in adults in 2012 (Cerebrovascular Accident and Transient Ischemic Attack) [30]. A standard of care for adults with TBI is developed in 2014 and for children with TBI in 2016 [29, 31]. The standard of care for children with TBI is partly suitable for use in children with nTBI, but a specific standard of care will be complementary for causes like hypoxic-ischemic events and brain tumors in children. Next step is to develop integrated care pathways for children and youth with ABI. These pathways have to be transparent in a closed chain of care. In TBI, a local (regional) protocol will be adequate which specifies elements of care in different settings, the sequence of care and expected patient progress over time [16, 29].

In integrated care pathways, child-directed and family-focused interventions in all phases of recovery play a vital role. Individualized psycho-education and adjustment to new circumstances are essential for optimal participation and HRQoL and to minimize family impact [32]. Further studies, like the Brains Ahead! study, explore the effects, intensity and timing of psychoeducation in mild TBI. Instructions how to return to previous activities and participation should be tailor-made and graded [33, 34].

RECOMMENDATIONS FOR FUTURE RESEARCH

Strengths and limitations of this thesis

The strength of this thesis is that it gives more insight in the long-term neurological outcome, participation, HRQoL and family impact in children and youth with ABI and the impact of predictors, based on a systematic review and a cross-sectional study.

A limitation of the cross-sectional study was the relatively high percentage of non-responders that may have caused selection bias. Since we checked, that the sample did not differ from the target population of children and youth with a hospital-based diagnosis ABI, we assume that the nonresponse did not seriously flaw generalizability of the results. A strength, but also a limitation of the cross-sectional study is time since onset: two years after diagnosis is a relatively long period in which many factors may influence outcome and it is a long period to reflect on. In order to improve the response rate and recall bias in future research, an additional assessment within the first year post-injury might be considered, preferably in a longitudinal design. Furthermore, a large percentage of

the children in the cross-sectional study has mild ABI not requiring treatment, but this is within the range that is generally reported in the population of children and youth with ABI. Generalizability of the results to children with ABI who are currently treated for the consequences is therefore limited.

Future research

There is a need for valid prognostic algorithms for long-term outcome of pediatric ABI. This asks for large numbers of participants and for combining child-specific, injury-related and socio-environmental predictors. This requires an interdisciplinary, multisectoral effort to compile a national database with a long-term follow up. Standardization of the multidimensional comprehensive diagnostics, treatment interventions, and follow-up assessment time-points may enhance reliability and validity of study comparisons and refine personalized treatment and care. This is aligned with international efforts to develop and implement standards for clinical research (Common Data Elements) [35] with a core set of child-specific, injury-related and socio-environmental predictors and routine outcome measures. A list of recommended core measures, as well as supplemental and emergence measures in pediatric TBI is described for several domains of functioning by the inter-agency Pediatric TBI Outcome Workgroup [36]. Research should identify modifiable predictors as this may help to improve outcome and to identify those who are most at risk for an unfavorable outcome and are likely to benefit from long term follow up.

In clinical practice it is challenging to use sensitive neuropsychological and age-appropriate tests at standard follow up moments to screen and monitor for deficits in functions and restrictions in activities and participation. Besides identifying changes in functions and activities we have to consider whether these changes are meaningful for child and parents. Age-appropriate tools, including neurological examination with short screening batteries (including measures of reaction time, visuospatial- and verbal working memory) for detecting cognitive problems are needed for use in Emergency Departments and in general practice [28, 37]. In the rehabilitation setting an extended battery of assessments is advised to measure motor, language, cognitive and behavioural functions, childrens' activities and participation and self-reported HRQoL of children and caregivers. Informed by the present study results and actual developments with computerized adaptive testing (CAT) instruments, these might include an extended neurological examination similar to the PSOM-SNE, clinical evaluation of language, an extended neuropsychological and behaviour assessment, in combination with patient reported outcomes (PROs) of participation, HRQoL and family impact.

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Samenvatting

Niet-aangeboren hersenletsel (NAH) is letsel(schade) aan de hersenen dat is opgelopen na de neonatale periode en geen gevolg is van een genetische of congenitale aandoening. Het is een veel voorkomende oorzaak van morbiditeit van kinderen en jongeren in de Westerse wereld. NAH kan worden ingedeeld in traumatisch hersenletsel (traumatic brain injury, TBI) en niet-traumatisch hersenletsel (non-traumatic brain injury, nTBI). De geschatte incidentie in Nederland voor de leeftijdsgroep 0–24 jaar is 585 per 100.000 voor traumatisch hersenletsel (15.000 nieuwe gevallen per jaar) en 190 per 100.000 voor niet-traumatisch hersenletsel (5.000 nieuwe gevallen per jaar). 10–15% van NAH in deze leeftijdsgroep wordt geclassificeerd als matig of ernstig letsel. Voor het classificeren van traumatisch hersenletsel wordt veelal de Glasgow Coma Scale (GCS) gebruikt (licht GCS 13–15, matig GCS 9–12, ernstig GCS <9). Niet-traumatisch hersenletsel kan worden geclassificeerd met de modified paediatric Ranking Scale (mRS) (licht mRS 0–1, matig mRS 2–3, ernstig mRS 4–5).

De afgelopen jaren is er een toename van wetenschappelijk onderzoek gericht op functiebeperkingen (stoornissen) ten gevolge van NAH bij kinderen en jongeren. Motorische, communicatieve, cognitieve en gedragsmatige problemen zijn gevolgen die een behoorlijke impact op de levensloop van kinderen en hun gezin kunnen hebben. Zelfs jaren na het hersenletsel kunnen deze stoornissen en problemen de participatie en gezondheidgerelateerde kwaliteit van leven negatief beïnvloeden. Wetenschappelijk onderzoek gericht op beperkingen in participatie en gezondheidgerelateerde kwaliteit van leven op lange termijn bij patiënten met NAH jonger dan 24 jaar is beperkt, evenals inzicht in voorspellers (determinanten) van deze betekenisvolle uitkomstmaten. Determinanten kunnen ingedeeld worden in kindfactoren, letselfactoren en omgevingsfactoren. In een systematisch literatuuronderzoek met vijf geïncludeerde studies tot 2012 werden de volgende determinanten voor beperkingen in participatie gevonden: een grotere ernst van het hersenletsel, problemen in motorische en sensorische functies, problemen in cognitieve of gedragsmatige functies, aanwezigheid van problemen in de toegankelijkheid en het ontwerp van de fysieke omgeving en het ontbreken van sociale acceptatie en steun. Er zijn geen systematische literatuuronderzoeken gepubliceerd over prognostische factoren in relatie tot participatie op lange termijn bij kinderen met TBI en er zijn twee systematische literatuuronderzoeken gericht op de relatie tussen prognostische factoren en kwaliteit van leven op lange termijn bij kinderen met TBI. Deze literatuuronderzoeken zijn beperkt tot studies gepubliceerd voor 2010 of alleen gericht op licht TBI. Er werd aangetoond dat tijdsduur na het letsel, leeftijd, premorbide problemen (kindfactoren), ernst van het letsel (letselfactor) en sociaaleconomische status (omgevingsfactor) determinanten waren voor gezondheidgerelateerde kwaliteit van leven op lange termijn.

Inzicht krijgen in determinanten voor toekomstig functioneren zijn van belang voor het maken van zorgpaden (integrated care pathways). Zorgpaden worden opgesteld door verschillende zorgverleners (multidisciplinair) om te kunnen anticiperen op de juiste zorg op het juiste moment zodat de patiënt zo veel mogelijk steun en zo min mogelijk gevolgen en beperkingen ervaart. Het identificeren van beïnvloedbare determinanten geeft de mogelijkheid om op het juiste moment te interveniëren en zodanig het toekomstig functioneren positief te beïnvloeden. Het is daarom van belang zowel premorbide determinanten als determinanten na het letsel op te sporen. Dit proefschrift richt zich op neurologisch functioneren, participatie en gezondheidgerelateerde kwaliteit van leven van kinderen en jongeren met licht, matig en ernstig NAH op lange termijn en factoren (determinanten) die hierop van invloed zijn. In hoofdstuk 6 en 7 hebben we de focus gelegd op kinderen met licht traumatisch hersenletsel.

Hoofdstuk 2 beschrijft de resultaten van een systematisch literatuuronderzoek naar de determinanten van beperkingen in participatie en verminderde gezondheidgerelateerde kwaliteit van leven op lange termijn (≥6 maanden) bij kinderen en jongeren met TBI. Er zijn 19 artikelen geselecteerd die 11 cohorten betreffen. De meest gebruikte uitkomstmaten voor participatie en gezondheidgerelateerde kwaliteit van leven (respectievelijk de Child and Adolescent Scale of Participation (CASP) en de Paediatric Quality of Life Inventory (PedsQL)) zijn gekozen als primaire uitkomstmaten.

Inconsequent bewijs werd gevonden voor leeftijd en ernst van het hersenletsel in relatie tot participatie. Er werd een sterke relatie gevonden tussen cognitieve problemen na het letsel en beperkingen in participatie. Door de variëteit van de onderzochte determinanten in relatie tot gezondheidgerelateerde kwaliteit van leven konden geen sterke conclusies worden getrokken. Er werd zwak bewijs gevonden dat zowel leeftijd als premorbide lichamelijke comorbiditeit geen relatie hebben met HRQoL op lange termijn. Inconsequent bewijs werd gevonden voor premorbide gezondheidsproblemen, depressie na het letsel, ernst van het letsel, letselgerelateerde comorbiditeiten, sociaaleconomische status, gezinsfunctioneren, soort ziektekostenverzekering en burgerlijke staat in relatie tot HRQoL op lange termijn. Geconcludeerd werd dat er longitudinale prospectieve studies nodig zijn die kindfactoren, letselfactoren en omgevingsfactoren als determinanten combineren om participatie en HRQoL te voorspellen op verschillende tijdstippen na het letsel.

Hoofdstuk 3 beschrijft een cross-sectionele follow-upstudie van een ziekenhuiscohort in Nederland waarbij neurologische stoornissen bij kinderen en jongeren (6–22 jaar) gemeten zijn twee jaar na het doorgemaakte NAH. Correlaties met kindfactoren, letselfactoren en omgevingsfactoren zijn bestudeerd, evenals relaties tussen neurologische stoornissen en beperkingen in participatie. Een gestandaardiseerd neurologisch onderzoek werd

afgenomen (Paediatric Stroke Outcome Measure Short Neuro Exam) om neurologische functiestoornissen te bepalen. Dit onderzoek bestaat uit 115 items waarbij het volgende is onderzocht: sensomotorische functies rechts en links, taalbegrip en taalproductie, cognitieve functies en gedragsmatige functies. Voorafgaand aan het neurologisch onderzoek, werd door ouders/verzorgers een vragenlijst ingevuld (CASP) om participatie in kaart te brengen op vier domeinen in relatie tot leeftijdsgenoten en een vragenlijst met betrekking tot de medische voorgeschiedenis en eventuele ontwikkelingsproblemen van hun kind voor het doorgemaakte NAH.

Eén op de drie kinderen met NAH heeft neurologische stoornissen twee jaar na het letsel, vooral sensomotorische en cognitieve stoornissen. nTBI en een lager schoolniveau waren ongunstige prognostische factoren voor neurologische stoornissen op lange termijn. Doorgemaakt nTBI was gerelateerd aan meer sensomotorische en taalstoornissen dan doorgemaakt TBI. Kinderen met een lager schoolniveau hadden significant meer cognitieve stoornissen. Er werd geen relatie gevonden tussen ernst van het hersenletsel (licht, matig of ernstig), leeftijd of omgevingsfactoren en de mate van neurologische stoornissen twee jaar na het letsel. Meer neurologische stoornissen en meer ernstige neurologische stoornissen waren gerelateerd aan meer beperkingen in participatie op alle domeinen, vooral op school.

In **hoofdstuk 4** wordt de HRQoL twee jaar na NAH beschreven bij kinderen en jongeren uit dezelfde studie zoals beschreven in hoofdstuk 3. HRQoL bij kinderen en jongeren werd vergeleken met gezonde Nederlandse kinderen van dezelfde leeftijd en werd vergeleken met de vragenlijst ingevuld door hun ouders/verzorgers. Relaties met kindfactoren, letselfatoren en omgevingsfactoren werden onderzocht. Kinderen en ouders vulden de Generic Core Scales van de PedsQL in die gezondheidgerelateerde kwaliteit van leven van hun kind op de volgende vier domeinen heeft gemeten: lichamelijke gezondheid, emotioneel functioneren, sociaal functioneren en functioneren op school.

Kinderen met licht tot ernstig NAH ervaren hun HRQoL goed twee jaar na het letsel, gelijk aan de Nederlandse referentiepopulatie van dezelfde leeftijd. Het merendeel van de kinderen had echter een licht hersenletsel doorgemaakt (88%), een percentage dat overeenkomt met de incidentie van ernst bij doorgemaakt hersenletsel. Op de leeftijd van 6–7 jaar en 13–18 jaar scoorden de ouders/verzorgers van kinderen met NAH significant lager op psychosociaal gebied vergeleken met de referentiepopulatie met name op gebied van emotioneel functioneren. Kinderen of jongeren met cognitieve, gedragsmatige of sociale problemen na het letsel hadden lagere HRQoL-scores op lange termijn, met name op psychosociaal gebied.

Hoofdstuk 5, eveneens gebaseerd op het zelfde cohort zoals beschreven in hoofdstuk 3 en 4, beschrijft de impact van NAH op het gezin twee jaar na het letsel en relaties met kindfactoren, letselfactoren en omgevingsfactoren. De impact op het gezin werd onderzocht met de Paediatric Quality of Life Inventory Family Impact Module (PedsQL FIM).

De gemeten impact in het gezin was aanzienlijk, vooral bij kinderen en jongeren met nTBI en was gerelateerd aan het niveau van functioneren twee jaar na NAH. nTBI, ernstiger nTBI en premorbide gezondheidsproblemen waren gerelateerd aan een hogere impact op het gezin.

In hoofdstuk 6 en 7 ligt de nadruk op kinderen en jongeren met licht TBI. In hoofdstuk 6 is dit een subgroep van het cohort beschreven in hoofdstuk 3 t/m 5. Hierin worden de uitkomsten op cognitief gebied in relatie tot participatie beschreven. Een neuropsychologisch onderzoek werd twee jaar na het letsel afgenomen, bestaande uit vier subtesten (op de computer) van de Amsterdam Neuropsychological Tasks (ANT) in combinatie met de Complexe Figuur Test van Rey met Recognitietrial en de Digit Span test met als doel subtiele cognitieve stoornissen te detecteren.

Twee jaar na het letsel waren cognitieve stoornissen aanwezig bij 7–15% van de kinderen en jongeren met licht TBI. Er werden beperkingen gevonden op het gebied van verwerkingssnelheid, inhibitie, cognitieve flexibiliteit, visueel-ruimtelijke oriëntatie/ structuratie en visueel-ruimtelijk geheugen. Schoolniveau en premorbide cognitieve problemen waren gerelateerd aan cognitieve problemen twee jaar na doorgemaakt licht TBI. Door ouders/verzorgers werd een verminderde participatie van hun kinderen met licht TBI aangegeven in relatie tot leeftijdsgenoten, 52–82% afhankelijk van het gemeten participatiedomein. Verminderde inhibitiesnelheid, beperkingen in visueel-ruimtelijk geheugen en verbaal werkgeheugen waren gerelateerd aan beperkingen in participatie.

Hoofdstuk 7 beschrijft het design van de Brains Ahead! studie, een gerandomiseerd onderzoek met controlegroep ingebed in een multicenter longitudinale prospectieve cohortstudie om inzicht te krijgen in welke kinderen met licht hersenletsel risico lopen op participatieproblemen op lange termijn. De Brains Ahead! studie is het vervolg op het onderzoek gepresenteerd in dit proefschrift. Kinderen en jongeren tussen de 6 en 18 jaar oud met licht TBI zijn twee weken na het letsel geïncludeerd in deze studie en kindfactoren, letselfactoren en omgevingsfactoren worden als determinanten onderzocht. Kinderen worden gerandomiseerd in een interventiegroep voor psycho-educatie of in een controlegroep. De interventie bestaat uit het geven van informatie over de gevolgen van licht TBI en het geven van adviezen gericht op copingstrategieën.

Tot slot bespreekt hoofdstuk 8 de belangrijkste bevindingen van het proefschrift, suggesties voor klinische toepassingen en aanbevelingen voor verder onderzoek.

About the author

Curriculum vitae
List of publications
PhD portfolio

CURRICULUM VITAE

Suzanne Lambregts was born on 22th of August in 1973 in Hoeven, the Netherlands. She passed her athenaeum at Thomas More College in Oudenbosch in 1991, studied Medicine at the University of Antwerp (RUCA) during one year (1991–1992) and continued her Medical study at the Vrije Universiteit (VU) of Amsterdam (1992–1998). In 1999–2000 she worked as resident in youth healthcare (GGD) Breda and as resident in Pediatrics at Amphia Hospital Breda. After working as resident in Child Psychiatry in Erasmus MC University Medical Centre (EMC) in Rotterdam she became resident in Rehabilitation Centre Blixembosch in Eindhoven until January 2002 after which she started her training in Rehabilitation Medicine in the departments of Sophia Rehabilitation Centre in The Hague, the Maasland Hospital in Rotterdam and the Leids University Medical Centre (LUMC) in Leiden. In Leiden and The Hague she followed concurrently a training in Child Orthopedics en Child Neurology. She obtained the degree of Medical Doctor in Physical and Rehabilitation Medicine in 2006 and she became certified as well by the European Board of Physical and Rehabilitation Medicine.

In 2006 she began working as pediatric physiatrist in Rijndam Rehabilitation Centre (location Westersingel) and the Department of Rehabilitation Medicine and Physical Therapy, Erasmus MC University Medical Centre in Rotterdam. In 2008 she became involved in research of children and youth with acquired brain injury. Since October 2010 she works at Revant Rehabilitation Centre in Breda, as pediatric physiatrist and started her work on this thesis.

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Bemmel JM, Loon-Felter AE, Kloet AJ, Damoiseaux J, Lambregts SAM, Hilberink SR, Roebroeck ME. Participation of children and young adults with acquired brain injury: two years after injury. Poster EACD, Wenen July 2014.

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PHD PORTFOLIO

Name PhD student:	S.A.M. Lambregts
Erasmus MC Department:	Rehabilitation Medicine
PhD period:	2010–2019
Promotor:	Prof. dr. G.M. Ribbers
Co-promotoren	Dr. M.E. Roebroeck
	Dr. C.E. Catsman-Berrevoets

PhD training	Year	Workload (hours/ECTS)
General courses		
Teach the Teacher module III	2011	14 / 0.5
Cursus introductie klinisch wetenschappelijk onderzoek	2012	8 / 0.3
Basistraining Toetsen op de werkplek	2015	6 / 0.2
BROK course (Basiscursus Regelgeving Klinisch Onderzoek)	2015	30 / 1
Motivational Interviewing	2016	24 / 1
Wat elke arts moet weten over statistiek	2016	12 / 0.4
Specific courses		
Scholing kinderrevalidatiegeneeskunde jaarlijks	2011–2019	162 / 6
Basiscursus Traumatisch hersenletsel	2012	6 / 0.2
Cursus GBA voor gevorderden	2013	10 / 0.4
Beweging in spasticiteit	2017	6 / 0.2
Cursus handorthese spastische hand	2018	6 / 0.2
Seminars and workshops		
Congres Opleiden is maatwerk	2013	6 / 0.2
Congres Samen Beter Hilversum	2015	4 / 0.2
Regionale ketenzorg	2017	4 / 0.2
Landelijke ouder-kinddag Zeist	2018	4 / 0.2
GGD	2019	4 / 0.2
Presentations		
Zonneveldlezing Zeeland	2012	4 / 0.2
Scholing kinderrevalidatieartsen	2013	4 / 0.2
Poster Presentation DCRM Harrogate	2013	4 / 0.2
Refereeravond Amphia	2013	2 / 0.1
Brain Awareness Week (BAW) Den Haag	2014	4 / 0.2
Poster Presentation IBIA San Francisco	2014	4 / 0.2
Vakgroep revalidatieartsen West Brabant/Zeeland	2014	2 / 0.1
Poster Presentation DCRM Rotterdam	2014	4 / 0.2
Huisartsengroep Breda Zuid	2014	2 / 0.1
Refereeravond Rijndam	2015	2 / 0.1
NAH onderzoekswerkgroep Den Haag	2015	4 / 0.2

PhD training	Year	Workload (hours/ECTS)
NAH lotgenoten avond Revant Breda	2016	2 / 0.1
Symposium Kinderafasie Rijndam Rotterdam	2017	4 / 0.2
Brain Awareness Week (BAW) Den Haag	2017	4 / 0.2
Poster Presentation EACD Amsterdam	2017	4 / 0.2
Regionale Themabijeenkomst Breda	2017	4 / 0.2
Regionale Themabijeenkomst Middelburg	2018	4 / 0.2
Breinlijn	2018	2 / 0.1
Huisartsenavond Amphia	2018	2 / 0.1
Poster Presentation EACD Parijs	2019	4 / 0.2
Invited symposium Revant	2019	4 / 0.2
(Inter)national conferences		
AACPDM Washington	2010	24 / 0.9
EACD Rome	2011	20 / 0.7
BAW Den Haag	2012	8 / 0.3
Congress Mastery of Manual Skills	2012	16 / 0.6
IBIA Edinburgh	2012	16 / 0.6
DCRM Harrogate	2013	10 / 0.4
IBIA San Francisco	2014	18 / 0.6
Symposium multitrauma	2014	2 / 0.1
DCRM Rotterdam	2014	8 / 0.3
BAW Den Haag	2015	5 / 0.2
VRA Lustrumcongres	2015	2 / 0.1
Toekomst Kinderrevalidatieonderzoek Nederland	2015	6 / 0.2
IBPIS Liverpool	2015	20 / 0.7
IBIA Den Haag	2016	8 / 0.3
Symposium netwerken en samenwerken	2016	3 / 0.1
EACD Amsterdam	2017	8 / 0.3
IBPIS Rome	2017	16 / 0.6
BAW Den Haag	2018	5 / 0.2
EACD Parijs	2019	6 / 0.2
Other		
Deelname landelijke werkgroep HeJ	2011–2019	54 / 2
Deelname landelijke onderzoeksgroep O&O	2011–2019	27 / 1
Deelname regionale refereergroep	2010–2019	19 / 0.7

Teaching	Year	Workload (hours/ ECTS)
Arts Verstandelijk Gehandicapten (AVG) opleiding	2013	8 / 0.3
AVG-opleiding	2014	4 / 0.2
AVG-opleiding	2015	4 / 0.2
Basiscursus revalidatiegeneeskunde Traumatisch Hersenletsel Rotterdam	2012	4 / 0.2
Circuitonderwijs AIOS revalidatie OOR-ZON	2013–2019	6 / 0.2
Supervising		
Research of Residents Rehabilitation Medicine on Department Rijndam and Erasmus Medical Centre	2010–2013	80 / 3
Medical Students (co-assistenten)	2018–2019	40 / 1.5
Residents Rehabilitation Medicine on Department child rehabilitation Revant Breda	2013–2018	260 / 9

Dankwoord

Het schrijven van een proefschrift is best een hele klus waar je gedrevenheid en doorzettingsvermogen voor nodig hebt, maar het helpt enorm als je het belang van het onderwerp voor ogen houdt en je je gesteund voelt door veel mensen om je heen. Daarom wil ik graag alle mensen bedanken die hebben bijgedragen aan de totstandkoming van dit proefschrift.

Alle deelnemende kinderen, jongeren en hun ouders

Speciale dank gaat uit naar de kinderen, jongeren en hun ouders die aan dit onderzoek hebben deelgenomen. Velen van hen waren niet eerder in contact gekomen met een revalidatiearts en waren zich niet bewust van mogelijke gevolgen van niet aangeboren hersenletsel op lange termijn. Ook veel dank aan de kinderen, jongeren en hun ouders die een foto hebben aangeleverd voor dit proefschrift.

Promotor, copromotoren en promotiecommissie

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Promotiecommissie

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Dirven, Prof. dr. Coen van Bennekom, Prof. dr. Annemiek Buizer en Dr. Marjolijn Ketelaar wil ik bedanken voor het plaatsnemen in de oppositiecommissie.

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Collegae

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