

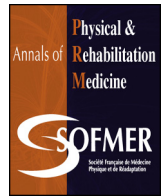


Available online at

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com



Original article

Young adults' perspectives on health-related quality of life after paediatric traumatic brain injury: A prospective cohort study

Nicholas P. Ryan^{a,b,c,d,e,*}, Kate Noone^a, Celia Godfrey^{a,d}, Edith N. Botchway^a,
Cathy Catroppa^{a,b,c,d}, Vicki Anderson^{a,b,c,d}

^a Brain & Mind Research, Clinical Sciences Theme, Murdoch Children's Research Institute, Melbourne, Australia

^b Psychological Sciences, University of Melbourne, Melbourne, Australia

^c Psychology Service, Royal Children's Hospital, Melbourne, Australia

^d Department of Paediatrics, University of Melbourne, Melbourne, Australia

^e Cognitive Neuroscience Unit, Deakin University, Geelong, Victoria, Australia

ARTICLE INFO

Article history:

Received 3 January 2019

Accepted 13 June 2019

Keywords:

Cohort study

Traumatic brain injury

Quality of life

Outcome

Young adulthood

ABSTRACT

Background: Quality of life (QoL) is commonly affected in children and families living with traumatic brain injury (TBI). Despite the established link between childhood TBI and reduced health-related QoL (HRQoL), there is a dearth of longitudinal, prospective research to determine the prevalence and predictors of impaired HRQoL in the very long term post-injury.

Objectives: We evaluated HRQoL in young adult survivors of paediatric TBI at 15 years post-injury. We aimed to identify the prevalence of impaired HRQoL and the respective contribution of pre-injury, environmental, injury-related, cognitive and mood-based factors to various dimensions of HRQoL at 15 years post-injury.

Methods: This prospective study involved 52 young adult survivors of mild to severe TBI included from consecutive hospital admissions to the Royal Children's Hospital between 1993 and 1997 who underwent neuropsychological evaluation and completed self-reporting measures of HRQoL, psychological functioning and social communication at 15 years post-injury.

Results: As compared with an age-matched Australian normative sample, the TBI group reported significantly poorer physical HRQoL at 15 years post-injury. Although group differences in other HRQoL domains did not reach statistical significance, 52% of the TBI group reported impaired functioning in at least one HRQoL domain. Contrary to expectations, HRQoL was not associated with injury severity, socioeconomic status, or pre-injury functioning. Instead, poorer HRQoL was linked to more severe depression symptoms, greater perceived social communication difficulty and reduced cognitive flexibility at 15 years post-injury.

Conclusions: A substantial proportion of young adult survivors of childhood TBI experience poor HRQoL in at least one domain of functioning at 15 years post-injury. These findings suggest that, even in the very long term post-injury, the identification and treatment of modifiable risk factors has potential to improve very-long-term HRQoL outcomes in this vulnerable population.

© 2019 Published by Elsevier Masson SAS.

1. Introduction

Traumatic brain injury (TBI) is a common cause of childhood death and disability and represents a significant, worldwide public

health issue [1]. In the Australian context, recent estimates suggest that 219 to 345 cases per 100,000 are reported annually [2]. These injuries are often associated with a range of physical, emotional, cognitive and social impairments, which may persist for many years post-injury and contribute to reduced quality of life (QoL) for children and their families [3–5].

Historically, studies of childhood TBI have relied heavily on functional outcome measures intended to assess the nature and extent of functional problems. These scales are best conceptualised as indices of functional status, and as such, are limited in their capacity to capture the child's subjective experience of problems

* Corresponding author at: Brain & Mind Research, Murdoch Children's Research Institute, 50, Flemington Road, Parkville, Victoria, 3052, Australia.

E-mail addresses: nicholas.ryan@mcri.edu.au (N.P. Ryan), kate.noone@mcri.edu.au (K. Noone), celia.godfrey@mcri.edu.au (C. Godfrey), edith.botchway@mcri.edu.au (E.N. Botchway), cathy.catroppa@mcri.edu.au (C. Catroppa), vicki.anderson@rch.org.au (V. Anderson).

and their perceptions of health and well-being [6]. More recently, measures of health-related QoL (HRQoL) are being increasingly incorporated into studies of childhood TBI, [5] a trend that mirrors a broader healthcare shift toward recognising the child's own perspective as central to evaluating post-injury outcomes [6].

According to the World Health Organisation (WHO), QoL is defined as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [7]". Because QoL is a broad, over-arching construct that may be affected by many factors, the concept of HRQoL has been developed to reflect an individual's perception of how illness and treatment factors influence various aspects of mental, social, and physical well-being [6].

As compared with studies of other childhood chronic health conditions, research into HRQoL after childhood TBI has been limited by small, cross-sectional, retrospective studies [5]. These studies report poor HRQoL associated with severe childhood TBI [3,4]. Other studies have identified universal HRQoL impairments, regardless of injury severity [8]. Overall, despite the putative association between childhood TBI and reduced HRQoL, longitudinal prospective research is lacking, and further studies are needed to examine HRQoL and its correlates in the very long term post-injury. Additionally, given the inconsistent links between HRQoL and TBI severity, further research is needed to identify non-injury-related factors that contribute to poor HRQoL and can be potentially modified via interventions to improve child outcomes.

Childhood TBI has been linked to a range of physical, cognitive and behavioural deficits that may contribute to poor subjective health and well-being [5]. TBI is commonly associated with both focal and diffuse brain pathology, which has downstream consequences for maturation of large-scale neural networks implicated in executive functioning, social cognition and pragmatic communication [9]. Deficits in executive functioning (e.g., inhibitory control, planning, cognitive flexibility) are evident immediately post-injury and often persist into the long term [10], likely reflecting delayed or arrested development of skills [11]. Because executive functions are necessary to anticipate the consequences of specific actions and recognise when certain behaviours are appropriate in a certain social context, deficits in these domains are likely to negatively impact the quality of interpersonal relationships, thereby contributing to a decline in subjective health and well-being [12].

Social communication skills are also commonly disrupted by childhood TBI and have potential to further impact perceived health and functioning [13]. Deficits in social interaction are particularly common in the context of frontal or diffuse childhood TBI [9,14] and may include difficulties in reading emotions from non-verbal social cues, inferring beliefs and intentions of others, conversational turn taking, and using language to meet changing social demands [15]. Although social communication impairments have been linked to reduced interpersonal effectiveness and psychological difficulties in the chronic phase of injury, [14,16] the potential contribution of these factors to HRQoL after childhood TBI is not well understood.

Injury-related neurocognitive impairments may contribute to poor health outcomes; however, the double hazard theory [17] posits that the effect of early brain injury interacts with the presence of pre-existing vulnerabilities to heighten the risk of unfavourable outcomes after TBI [18]. This theory would predict that pre-injury environmental vulnerabilities (e.g., low socioeconomic status, parent mental health problems) and poor pre-injury child functioning (e.g., poor adaptive skills) contribute to poor long-term health outcomes, but the impact of these factors on very-long-term HRQoL outcomes has not been examined.

The Heuristic Model of Social Competence in Brain Disorder (HMSC) [12] provides a useful heuristic for conceptualizing how a range of injury, child-related and non-injury factors might interact dynamically and contribute to poor long-term functioning after childhood TBI. HMSC provides a useful framework to apply to the study of HRQoL. In this model, injury-related variables, including more severe injury and younger age of injury, are conceptualized as risk factors that increase the likelihood of poor long-term health outcomes. Additionally, pre-injury child and family environmental vulnerabilities may interact dynamically with injury factors to further exacerbate the risk of unfavourable health outcomes [12]. This model also depicts interrelationships between cognition and behaviour, such that post-injury deficits in any aspect of social communication or executive function contribute to impaired social adjustment and reduced HRQoL [12]. Although this model receives empirical support from studies of behavioural outcomes of childhood TBI, [14] HMSC has yet to be empirically validated for predicting post-injury HRQoL outcomes.

The objectives of the current investigation were to:

- evaluate HRQoL outcomes (including rates of impairment) among young adult survivors of mild to severe child TBI;
- determine the respective contribution of pre-injury, environmental, injury-related, cognitive and mood-related factors to various dimensions of HRQoL at 15 years post-childhood TBI.

More specifically, guided by the HMSC model, we aimed to examine the association of HRQoL to:

- pre-injury adaptive functioning;
- pre-injury socioeconomic status and family functioning;
- injury severity;
- executive functioning;
- pragmatic communication;
- depression symptom severity.

We hypothesized that as compared with an age-matched Australian normative sample, young adult survivors of TBI would report significantly poorer HRQoL at 15 years post-injury. Furthermore, we hypothesized that poorer HRQoL would be related to:

- worse pre-injury adaptive functioning;
- lower socio-economic status and poorer pre-injury family functioning;
- more severe injury;
- poorer executive function, including reduced cognitive flexibility;
- greater perceived social communication difficulty;
- greater depressive symptomology at 15 years post-injury.

2. Materials and Methods

2.1. Participants

This investigation forms part of a larger longitudinal prospective study [11] examining long-term outcomes of children with TBI and reports on the outcomes of this cohort at 15 years post-injury. For the original study, children with TBI were recruited through consecutive admissions to the Emergency Department of the Royal Children's Hospital between 1993 and 1997 [11]. Children were screened according to several inclusion criteria [11]:

- age 1–12 years;
- established medical diagnosis of TBI, including altered consciousness;
- medical information available to determine TBI severity.

Children were excluded on the basis of previous closed head injury, penetrating or non-accidental brain injury, and/or pre-existing neurodevelopmental or acquired brain disorder.

The original study involved 172 children with a diagnosis of TBI. At the 15-year follow-up, 66 participants were untraceable, 38 declined invitations, 2 had died, and 14 had incomplete HRQoL data. Of the 2 participants who died, the cause of death was suicide in one and the family did not disclose the cause of death in the other. Therefore, the current study reports on the outcomes of 52 young adult survivors of childhood TBI. High rates of sample attrition are typical in longitudinal studies of TBI, especially in young-age samples [18]. To identify potential sample attrition bias, we compared participating and non-participating groups at 15 years post-injury on a range of pre-injury, demographic and injury characteristics that could influence outcomes.

2.2. Measures

Medical, developmental, and family demographic information was collected via parent questionnaires and a review of child medical records conducted with local ethics approval. As described in previous reports, [11] TBI severity was established by the Glasgow Coma Score (GCS) [19] on admission and the presence or absence of radiological and neurological findings.

Using these metrics, participants were assigned to the following TBI severity categories:

- mild TBI ($n = 15$): GCS 13–15, with no evidence of mass lesion on clinical brain CT/MRI, and no neurological deficits;
- moderate TBI ($n = 26$): GCS 9–12, and/or presence of mass lesion or other specific injury on clinical CT/MRI, and/or neurological deficits;
- severe TBI ($n = 11$): GCS 3–8, and presence of mass lesion or other specific injury on clinical CT/MRI and/or neurological deficits.

2.3. Predictor variables

Pre-injury child functioning was assessed by the Vineland Adaptive Behavior Scales (VABS), [20] a parent questionnaire designed to assess a child's level of adaptive functioning. During initial recruitment into the study, parents were asked to retrospectively rate their child's pre-injury adaptive function on the VABS. In this report, we used the Total Adaptive Behavior score (mean 100 [SD] 15) as a measure of pre-injury function.

Pre-injury family functioning was measured by the Family Functioning Questionnaire (FFQ), [21] which uses parent ratings of family behaviour on a scale from 1 (totally agree) to 6 (totally disagree). The measure is used to derive a well-validated intimacy score, a higher score denoting higher levels of family cohesion and intimacy. The measure is reported to have good construct validity and excellent internal consistency (Cronbach alpha = 0.92) [21].

Pre-injury socio-economic status was assessed by the Daniel's Scale of Occupational Prestige [22]. On this scale, parent occupations are converted to a position on a 7-point scale, a lower score representing higher socio-economic status.

2.3.1. Acute intellectual functioning

IQ was assessed by using one of the following measures depending on the child's age:

- Cognition subscale, Bayley Scales of Infant Development (< 2.5 years);
- Full Scale IQ, Wechsler Preschool and Primary Scale of Intelligence-Revised (2.5–6.5 years);
- Full Scale IQ, Wechsler Intelligence Scale for Children, Third Edition (> 6.5 years).

All measures were standardised (mean 100 [SD] 15).

2.3.2. Executive functions

The Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (DKEFS) [23] was used to assess inhibitory control and cognitive flexibility. Conditions 3 and 4 of the CWIT are purported to measure cognitive inhibition and cognitive flexibility, respectively. In Condition 3, the examinee is shown rows of words printed in dissonant ink colors and asked to say the color of ink the words are printed in and not read the words as quickly as possible. In Condition 4, participants are provided a card that contains several rows of words printed in dissonant ink colors. Importantly, a proportion of the printed words are located within black rectangles. In this task, the participant is required to conform to 2 separate task rules. First, if the word is not contained within a black rectangle, the participant is instructed to name the color of ink the words are printed in. Second, if the word is contained within a black rectangle, the participant is instructed to read the word instead of naming the color of ink. The CWIT is a timed measure, such that the examinee is required to complete the task as quickly as possible, moving from left to right across the page. Standard scores (mean 10 [SD] 3) were used in analyses.

2.3.3. Pragmatic communication

The Latrobe Communication Questionnaire (LCQ) [24] is a 30-item self-reporting questionnaire that assesses perceived communication difficulty across 4 core domains: quantity, quality, relation and manner of everyday communication. Participants are required to rate the frequency of each problem on a 4-point scale, ranging from 1 ("never or rarely") to 4 ("usually or always"). Higher scores on the LCQ denote more frequent communication difficulty. The LCQ has been used extensively in studies of adult TBI and appears to be sensitive to long-term difficulties in this population. Previous reports suggest that the LCQ has excellent internal consistency (Cronbach alpha = 0.85), and ratings display good stability over time ($r = 0.76$) [24]. The LCQ has robust Australian normative data, collected from a sample of 147 healthy young adults aged 16 to 39 years [24]. Using the recommended clinical cutoff score, [24] 23.5% of the current TBI sample fell within the clinically significant range. Chi-square analysis revealed no relation between the TBI severity group and the presence of impairment on the LCQ ($P = 0.196$).

2.3.4. Depression symptoms

The General Health Questionnaire (GHQ) [25] is a 28-item self-reporting inventory that assesses psychological distress across 4 dimensions:

- depression symptoms;
- anxiety;
- social dysfunction;
- somatic symptoms.

Respondents rate each item on a scale of 1 to 4, with 4 indicating higher levels of psychological distress. The current study used the depression scale as an index of depression symptom severity.

2.4. Primary outcome

HRQoL was assessed at 15 years post-injury by using the WHOQOL-BREF-Australian version [26]. The WHOQOL-BREF is a 26-item version of the original instrument (WHOQOL-100) and assesses perceived functioning across 4 HRQoL domains: physical health, social relationships, psychological health, and environment. Individual items are rated on a 5-point Likert-scale, with each question designed to probe the respondent's perceived satisfaction with various aspects of their life [27]. Items are added for a total score for each domain, with maximum of 100. The physical health scale includes items relating to mobility, sleep quality and energy levels, the impact of pain on everyday performance, perceived level of reliance on medical treatment to function in everyday activities, and satisfaction with working capacity. The psychological health scale contains items that assess difficulties with concentration, self-esteem, frequency of unhelpful thoughts and feelings (i.e., low mood, anxiety), body image, and the extent to which the respondent perceives their life as meaningful. The social relationships scale examines the respondent's satisfaction with social support systems, personal relationships, and their sex life. The environment domain assesses perceived safety and security in the home and community, healthcare availability and accessibility of leisure activities and transport, and satisfaction with the home and physical environment [27]. Higher scores for each domain indicate better HRQoL. Each of the 4 domains demonstrate good internal consistency (Cronbach alpha = 0.60–0.90), excellent test–retest reliability (Pearson's $r > 0.80$ for each domain) and good construct validity. Previous research has shown that the WHOQOL-BREF score is correlated very strongly with WHOQOL-100 domain scores [28].

2.5. Procedure

The current study received ethical approval from the Human Research Ethics Committee (HREC) of The Royal Children's Hospital, Melbourne, Australia. Participants were recruited into the longitudinal study during their initial hospital admission and were followed up 7 times after TBI [29]. At each time, all families from the original study were contacted and were given a detailed description of the study. In keeping with local ethics procedures, families were required to provide written informed consent. At the 15-year follow up, a registered psychologist administered neuropsychological assessments and self-reporting inventories to each enrolled participant.

2.6. Data analysis

SPSS v23.0 (SPSS, Inc., Chicago, IL) was used for data analysis. Given the exploratory nature of the study and the need to minimize the risk of type 2 error, the alpha level was set to 0.05. One-way between-participants ANOVA was used to compare participating and non-participating groups in terms of injury, socio-demographic and clinical variables collected at initial recruitment and the effect of injury severity on WHOQOL-BREF domain scores. For primary outcome analyses, independent-samples Student t test was used to evaluate mean differences between the TBI study cohort and the age-matched Australian normative sample.

Individual impairment ratings were derived from WHOQOL-BREF-Australian population norms, [26] and Chi^2 tests were used to examine the proportion of individuals who fell within the impaired range across each TBI severity group. For each of the 4 WHOQOL-BREF domains, impairment was defined as a score > 1 SD below the age-matched Australian normative

sample mean [26]. In both the pediatric and adult HRQoL literature, QoL domain scores at least 1 SD below the population mean can help identify individuals at risk for impaired HRQoL [26,30–32]. Because such scores represent scores similar to those obtained by individuals living with severe chronic health conditions [32]. This 1-SD criterion is also in keeping with the cutoff score derived from the original psychometric validation study of the WHOQOL-BREF [26].

Predictors of HRQoL were assessed by univariate regression analysis to examine associations between WHOQOL-BREF domains and a range of theoretically relevant pre-injury, environmental, injury-related, cognitive and mood-related factors. Variables that significantly ($P < 0.05$) contributed to HRQoL at this step were included in multivariable adjusted regression models to identify associations between variables and each HRQoL domain.

3. Results

3.1. Sample attrition analyses

To identify potential sample attrition bias, we compared participating ($n = 52$) and non-participating ($n = 120$) groups at 15 years post-injury on a range of pre-injury, socio-demographic and injury characteristics. Specifically, these attrition analyses concerned identifying potential group differences on important preinjury characteristics (i.e., pre-injury family functioning, pre-injury child adaptive skills, and sex); injury characteristics (injury age, lowest GCS, mechanism of injury, presence of acute imaging abnormalities and need for acute surgical intervention); and post-acute cognitive factors (verbal, performance and full-scale IQ at 0–3 months post-injury). At the overall group level, participating and non-participating groups did not differ ($P > 0.10$), with the exception of fewer males participating in the 15-year follow-up ($\chi^2(10, n = 172) = 5.16, P = 0.02$).

We also conducted attrition analyses of participating and non-participating groups for each TBI severity group. For the mild and severe TBI groups, the 2 groups did not differ on measures of pre-injury family functioning and child adaptive skills, injury characteristics, or post-injury intellectual function ($P > 0.21$ in all group comparisons). The moderate TBI group showed similar findings; however, as compared with the non-participating group, the participating group had significantly higher verbal intelligence at 0 to 3 months post-injury ($P = 0.043$). The proportion of males was lower in the participating than non-participating group ($P = 0.017$). No other significant group differences were identified for pre-injury, injury or post-injury intellectual variables ($P > 0.31$ in all comparisons).

3.2. Sample characteristics

Table 1 displays key demographic characteristics of the TBI severity groups. The groups did not differ significantly on injury age, age at assessment, socioeconomic status or full-scale IQ. Injury characteristics of the TBI severity groups are in Table 2. As expected, GCS significantly differed between the groups. Children with severe TBI were more likely to require surgical intervention and have abnormal CT/MRI findings than other groups. Cause of injury differed between the injury severity groups: motor vehicle accidents were more frequent with severe TBI than other groups. Children with milder brain injuries more frequently experienced falls and/or blows to the head than other children.

Table 1

Demographic characteristics of young adults with a history of childhood traumatic brain injury (TBI).

	Mild TBI (n = 15, 28.9%)	Moderate TBI (n = 26, 50.0%)	Severe TBI (n = 11, 21.2%)	F/χ^2	p
Male, n (%)	8 (53.3)	15 (57.7)	5 (45.5)	0.47	0.79
Age at injury (years), mean (SD)	7.23 (3.5)	7.3 (3.0)	6.9 (3.3)	0.06	0.94
Range	2.8–12.3	2.0–12.1	2.5–12.8		
Age at 15-year follow-up (years), mean (SD)	23.59 (4.1)	24.0 (3.7)	23.3 (4.0)	0.16	0.85
Range	17.8–30.6	16.3–29.3	17.6–30.0		
SES acute, mean (SD)	3.9 (0.8)	4.4 (0.9)	4.3 (1.3)	1.30	0.28
FSIQ acute, mean (SD)	102.0 (14.6)	102.9 (13.2)	91.0 (16.8)	2.82	0.07
FSIQ at 15-year follow-up, mean (SD)	104.4 (19.9)	104.6 (12.3)	102.6 (10.4)	0.08	0.92
Self-reported problems at 15-year follow-up					
Speech problems, n (%) indicating “Yes”	1 (7)	8 (31)	2 (18)	5.48	0.24
Fine motor problems, n (%)	0 (0)	4 (15)	4 (36)	11.07	0.026
Gross motor problems, n (%)	1 (7)	4 (15)	4 (36)	8.27	0.082

SES: socio-economic status; FSIQ: Full Scale IQ.

Table 2

Injury characteristics young adults with a history of childhood TBI.

Injury characteristics	Mild TBI (n = 15)	Moderate TBI (n = 26)	Severe TBI (n = 11)	F/Fisher's exact test	P
Medical characteristics					
GCS on admission, mean (SD)	14.4 (1.2)	11.08 (3.4)	6.36 (1.4)	30.30	< 0.001
Neurological abnormalities, n (%)	0	11 (42.3)	10 (90.9)	24.02	< 0.001
Surgical intervention, n (%)	0	11 (42.3)	8 (72.7)	16.84	< 0.001
Abnormal CT/MRI, n (%)	0	20 (76.9)	10 (90.9)	31.71	< 0.001
Cause of injury, n (%)			14.06	0.05	
Motor vehicle accident	2 (13.3)	8 (30.8)	7 (63.6)		
Falls/blows	13 (86.7)	18 (69.2)	4 (36.4)		

GCS: Glasgow Coma Scale.

3.3. HRQoL at 15 years post-TBI

3.3.1. TBI versus normative sample

Table 3 compares the TBI group and the age-matched Australian normative sample on the WHOQOL-BREF domain scores [26]. As compared with the normative sample, the TBI group showed significantly worse HRQoL only in the physical health domain.

3.3.2. Outcome by severity

TBI severity groups did not significantly differ on any of the HRQoL domains (Table 4).

3.3.3. Rates of impairment

We examined the proportion of the TBI group within the impaired range on the HRQoL subscales, defined by a score > 1 SD below the mean for the age-matched Australian normative sample. Rates of impairment ranged from 17.3% (environment HRQoL) to 40.4% (physical HRQoL) (Table 5). Of note, 52% of the TBI sample reported impaired functioning in at least one HRQoL domain. Rates of impairment did not significantly differ between the TBI severity groups (Table 5).

3.4. Predictors of HRQoL on 4 WHOQOL-BREF domains

Univariate analyses revealed significant associations between physical HRQoL and depression symptom severity ($F(1,51) = 9.927$,

$P = 0.003$) and frequency of perceived social communication difficulty ($F(1,50) = 12.814$, $P < 0.001$). The adjusted model was highly significant ($F(2,50) = 7.681$, $P = 0.001$). On multivariable analysis, increased perceived social communication difficulty was the sole predictor of poorer physical HRQoL (Table 6).

Univariate analyses revealed significant associations between psychological HRQoL and frequency of perceived social communication difficulty ($F(1,50) = 25.685$, $P < 0.001$) and depression symptom severity ($F(1,51) = 36.982$, $P < 0.001$). The adjusted model was highly significant ($F(2,50) = 24.054$, $p < 0.001$). On multivariable analysis, poorer psychological HRQoL was associated with more severe depressive symptoms and greater perceived social communication difficulty (Table 6).

Univariate analyses revealed significant associations between social HRQoL and depression symptom severity ($F(1,51) = 20.194$, $P < 0.001$) and frequency of perceived social communication difficulty ($F(1,50) = 11.293$, $P = 0.002$). The adjusted model was highly significant ($F(2,50) = 11.423$, $P < 0.001$). On multivariable analysis, more severe depressive symptoms was the sole predictor of poorer social HRQoL (Table 6).

Univariate analyses revealed significant associations between environment HRQoL and acute full-scale IQ ($F(1,50) = 5.371$, $P = 0.025$), depression symptom severity ($F(1,51) = 14.501$, $P < 0.001$), frequency of perceived social communication difficulty ($F(1,50) = 16.029$, $P < 0.001$), and cognitive flexibility, ($F(1,51) = 5.168$, $P = 0.028$). The adjusted model was highly significant ($F(2,50) = 11.423$, $P < 0.001$). On multivariable analysis, poorer environment HRQoL was associated with more severe depressive symptoms and reduced cognitive flexibility (Table 6).

4. Discussion

Diminished quality of life is a common experience for children and families living with TBI. Despite the established link between childhood TBI and reduced HRQoL, there has been a dearth of prospective research to determine the prevalence and predictors of

Table 3

Health-related quality of life (HRQoL) domains by the WHOQOL-BREF for the TBI group and age-matched Australian normative sample (control).

HRQoL domain	TBI (n = 51)	Control (n = 147)	t	P value
Physical	77.2 (16.2)	85.4 (10.9)	2.928	0.004
Social	70.9 (17.2)	72.9 (18.8)	0.561	0.576
Psychological	68.9 (17.9)	71.4 (17.5)	0.715	0.475
Environment	75.4 (13.9)	74.3 (14.0)	0.399	0.690

Data are mean (SD). Items are added for a total score for each domain with maximum of 100.

Table 4
HRQoL by TBI severity.

HRQoL domain	Mild TBI (n = 15)	Moderate TBI (n = 26)	Severe TBI (n = 11)	df	F	P	ES
Physical	78.5 (10.7)	75.3 (19.4)	79.8 (14.5)	2, 52	0.364	0.697	0.015
Psychological	68.2 (17.0)	69.5 (17.8)	68.3 (20.7)	2, 52	0.030	0.971	0.001
Social	72.2 (15.3)	70.6 (17.3)	69.7 (20.7)	2, 52	0.070	0.932	0.003
Environmental	74.7 (9.9)	76.2 (15.0)	74.7 (16.5)	2, 52	0.070	0.933	0.003

Data are mean (SD). ES: effect size quantified by using partial eta squared. Items are added for a total score for each domain with maximum of 100.

Table 5
Percentage impaired by injury severity.

HRQoL domain	Total sample (n = 52)	Mild TBI (n = 15)	Moderate TBI (n = 26)	Severe TBI (n = 11)	χ^2	P value
Physical	21 (40.4)	6 (40.0)	10 (38.5)	5 (45.5)	0.158	0.924
Psychological	12 (23.1)	4 (26.7)	5 (19.2)	3 (27.3)	0.435	0.805
Social	12 (23.1)	4 (26.7)	6 (23.1)	2 (18.2)	0.257	0.879
Environmental	9 (17.3)	2 (13.3)	4 (15.4)	3 (27.3)	0.996	0.608

Data are n (%).

Table 6
Predictors of HRQoL dimensions: final adjusted models.

	β	B (SE)	95% CI	P value
Model 1: Physical				
LCQ self-report 15 years	–0.333	–0.382 (0.17)	[–0.73, –0.04]	0.031
GHQ depression 15 years	–0.224	–2.540 (1.70)	[–5.96, 0.88]	0.142
Model 2: Psychological				
LCQ self-report 15 years	–0.329	–0.418 (0.15)	[–0.73, –0.11]	0.009
GHQ depression 15 years	–0.472	–5.937 (1.53)	[–9.01, –2.86]	<0.001
Model 3: Social				
LCQ self-report 15 years	–0.194	–0.236 (0.17)	[–0.58, 0.11]	0.178
GHQ depression 15 years	–0.438	–5.295 (1.71)	[–8.74, –1.86]	0.003
Model 4: Environment				
Acute FSIQ	0.071	0.063 (0.12)	[–0.18]	0.597
LCQ self-report 15 years	–0.256	–0.256 (0.16)	[–0.58]	0.115
DKEFS: Inhibition/switching	0.277	1.776 (0.84)	[0.07]	0.042
GHQ depression 15 years	–0.369	–3.512 (1.44)	[–6.43, –0.59]	0.020

LCQ: Latrobe Communication Questionnaire; GHQ: General Health Questionnaire; FSIQ: Full Scale IQ; SE: standard error; 95% CI: 95% confidence interval.

impaired HRQoL in the very long term post-injury. To address this substantial gap in knowledge, this study evaluated HRQoL in young adult survivors of childhood TBI at 15 years post-injury. We aimed to identify the prevalence of impaired HRQoL and evaluate the respective contribution of pre-injury, environmental, injury-related, cognitive and mood-related factors to various HRQoL dimensions at 15 years post-injury.

Overall, we found partial support for expectations. As compared with the age-matched Australian normative sample, the TBI group reported significantly poorer physical HRQoL at 15 years post-injury. Although group differences in other HRQoL domains did not reach statistical significance, 52% of the TBI sample reported impaired HRQoL in at least one domain as measured by the WHOQOL-BREF. Contrary to expectations, HRQoL was not associated with injury severity, socioeconomic status, or pre-injury child and family functioning. Instead, the poorest HRQoL outcomes were associated with more severe depression symptoms and reduced cognitive flexibility at 15 years post-injury.

4.1. HRQoL outcomes: relation to injury factors

Our study suggests that by young adulthood, survivors of childhood TBI report significantly worse physical HRQoL as compared with the age-matched Australian normative sample. Consistent with this finding, the greatest rates of individual impairment were in the WHOQOL-BRIEF physical domain. Previous research has shown that residual physical disabilities are not uncommon in the long term after paediatric TBI, [33,34]

and our TBI sample is not an exception to this general trend. Of note, even at 15 years post-injury, 17% of our TBI sample reported some level of current gross motor dysfunction, and 35% reported current or previous involvement with physiotherapy services. Therefore, elevated rates of impaired HRQoL in the physical domain may be at least in part due to the ongoing physical limitations experienced by our TBI sample.

In addition to elevated rates of impairment in the HRQoL physical domain, analyses of individual impairment ratings showed that 1 in 2 young adult survivors of child TBI experience poor HRQoL in at least one domain of function. These results are broadly consistent with previous evidence of an association between TBI and reduced HRQoL in the chronic phase of childhood TBI [3,4] and suggest that more than 50% of young adult TBI survivors perceive significant functional difficulties in the very long term post-injury.

Contrary to our predictions and counter to previous studies linking worse HRQoL to more severe TBI, [3,4] impaired HRQoL was equally common across all levels of TBI severity. Similarly, comparison of group means failed to reveal the expected dose-response relation between TBI severity and HRQoL outcomes. These results run counter to previous findings of a dose-response relation between acute TBI severity and cognitive/intellectual outcomes in this same cohort at 10 years post-injury [35]. Nevertheless, the current 15-year outcome study focused primarily on psychosocial as opposed to cognitive outcomes, and this discrepancy in findings is largely consistent with evidence from the broader childhood TBI literature [36]. Specifically, there is

emerging evidence suggesting that post-TBI cognitive/intellectual outcomes are more tightly linked to injury factors, [37] whereas psychosocial outcomes are more closely related to family environmental factors (e.g., parent mental health, family affective dynamics) and child-related factors (e.g., executive function, theory of mind) [16,35,36]. The non-significant effect of acute TBI severity on HRQoL is also broadly consistent with studies of recovery in other domains of function, which suggests that the effect of TBI severity on outcome appears to diminish with increasing time after injury [38]. Moreover, these results converge with a small number of studies examining HRQoL outcomes in chronic-phase TBI, [8] suggesting that initial clinical indicators of TBI severity have reduced predictive value for very-long-term HRQoL outcomes, at least in the context of injury to the immature brain [39].

Similarly, the non-significant effect of age at injury on HRQoL outcomes likely reflects our exclusive focus on subjective perceptions of health and well-being. Specifically, because we relied exclusively on self-reports of TBI survivors, the null finding may be explained by respondent-related factors, including potential cognitive impairment and impaired self-awareness among survivors of more severe TBI as well as the degree to which younger participants can recollect pre-injury functioning. In particular, participants injured at a younger age may have fewer recollections of pre-injury functioning as compared with older children, who may be more able to reflect on loss of previously acquired skills.

4.2. HRQoL outcomes: relation to non-injury factors

Although injury-related factors did not significantly contribute to HRQoL, increased perceived social communication difficulty was associated with poor HRQoL, even after adjusting for depression symptom severity. Because pragmatic communication difficulties are relatively common in the very long term post-injury [13,16] and have been linked to damage of frontal-limbic brain circuits implicated in social cognition, [14] leading theoretical frameworks from social neuroscience provide a useful lens to interpret these findings. In keeping with the HMSC model, [12] pragmatic communication difficulty likely affects the quality and frequency of social interactions, thereby contributing to reduced interpersonal effectiveness [16]. Consequently, perceived successive failure to manage routine social interactions likely elicits chronic distress and contributes to a decline in subjective health and well-being [12].

Similarly, we found reduced HRQoL linked to poor cognitive flexibility. As described earlier, cognitive flexibility is commonly vulnerable to disruption due to childhood TBI [40] and involves the ability to disengage from a previous strategy, generate a new response set, and incorporate the new strategy into the task at hand [41]. The current finding is broadly consistent with previous research linking better cognitive flexibility to favourable outcomes across the adult lifespan, including resilience to negative life events and better overall quality of life [42]. Given that cognitive flexibility enables successful adaptation to changing circumstances and novel environmental demands, it is perhaps not surprising that we found difficulties in this domain linked to poor perceived health and well-being in our TBI sample. Given the evidence to implicate cognitive flexibility as a key mechanism underlying treatment success of cognitive behavioural therapy, [43] our findings might underscore the potential utility of cognitive behavioural therapy-based approaches (including problem-focused coping strategies) for optimising QoL in young adult survivors of childhood TBI.

Finally, we found that increased concurrent depression symptoms contributed to poor HRQoL across the social, psychological and environmental domains. This finding is consistent with

previous research, [44] which documents poor HRQoL among childhood TBI survivors endorsing high levels of psychological distress. Importantly, these results suggest the potential to improve HRQoL outcomes by addressing modifiable risk factors, including depression symptoms. This is particularly important given that that psychological sequelae are commonly documented in the many years post-injury [38] and may be amenable to change with pharmacological and non-pharmacological interventions, including cognitive behavioural therapy [45].

Despite evidence for robust relationships between HRQoL, mood-based factors, and perceived social communication difficulty, our findings should be interpreted with some caution. Specifically, these relationships were detected by using questionnaire-based measures administered concurrently to the same respondent. These strong relationships agree with study hypotheses and with current conceptual models of psychosocial outcome after TBI, [12] but we cannot rule out that respondent-related factors explain at least in part the high shared variance between self-reporting questionnaire measures collected at the same time [46]. For instance, previous studies have offered empirical support for the notion that respondent-related factors (i.e., personality and emotional factors) influence symptom reporting on self-reporting measures assessing distinct constructs [47,48]. In the current study, respondent-related variables might underlie some of the observed associations that were not entirely expected. For example, the impact of perceived social communication difficulty on physical HRQoL is explained at least in part by respondent-related factors. Nevertheless, because the WHOQOL-BREF physical scale is a broad-based measure that includes items relating to satisfaction with sleep, capacity for work and ability to perform daily activities, it is not entirely surprising that perceived difficulty with social communication might affect functioning in this domain.

4.3. Non-significant effect of sex on HRQoL

The non-significant effect of sex on HRQoL is somewhat surprising and contrasts with previous findings linking female sex to poor HRQoL in patients with a history of paediatric cancer, [49] TBI [50] and cystic fibrosis [51]. In the current study, the null finding might be explained at least in part by the significantly lower proportion of males in the participating versus non-participating TBI group at 15 years post-injury. As such, the non-significant effect of female sex on HRQoL should be interpreted with caution.

4.4. Limitations

To our knowledge, our study represents the longest running prospective study of childhood TBI outcomes to date; however, the strength of our findings was weakened by the relatively small sample ($n = 52$). Longitudinal prospective studies of this nature are prone to sample attrition, and our sample was no exception [52]. Attrition analyses within TBI severity groups revealed that for the moderate TBI group only, verbal intelligence at 0 to 3 months post-injury was significantly higher in the participating than non-participating group. Although speculative, this pattern of findings suggests that our current results provide a conservative estimate of HRQoL impairment among individuals with moderate TBI.

The strength of the current findings is also weakened by the absence of an orthopaedic injury control group. Indeed, there is considerable debate concerning brain-injury-specific effects versus general-injury effects on outcomes after TBI. For instance, some research has found that chronic symptom burden and/or abnormal neuropsychological functioning after mild TBI are attributable to premorbid or environmental determinants that are common to many types of injuries, including orthopedic

injuries [37,53–56]. Given the absence of an orthopaedic-injury control group, we cannot establish whether elevated rates of impaired HRQoL in our sample are unique to individuals with a history of neurological trauma (i.e., a brain-injury-specific effect) or whether these long-term outcomes are explained at least in part by pre-existing risk factors (e.g., premorbid psychiatric problems) that are shared by children who sustain orthopaedic and neurological trauma. Nevertheless, despite this important limitation, our prospective study involved the collection of detailed information regarding pre-injury functioning assessed by using retrospective parent reports of pre-injury function collected at the time of injury. Limited evidence for a dose–response relation between injury severity and HRQoL may point to the potential contribution of premorbid factors to variation in long-term outcomes, but no such associations were detected in our sample. Namely, measures of pre-injury family functioning and premorbid child adaptive functioning did not contribute to long-term HRQoL outcomes in our sample.

A further limitation relates to our sole reliance on patient self-reports of subjective health and well-being. Given that patient self-awareness and insight can influence self-reported ratings, we cannot rule out the potential impact of these variables on the observed pattern of finding [57]. Given this important caveat, the non-significant effect of injury severity on HRQoL outcome should be interpreted with caution.

Finally, because of the initial primary aim of the current longitudinal study, previous time points focused almost exclusively on assessment of intellectual and cognitive outcomes. Therefore, we could not examine longitudinal trajectories of HRQoL after childhood TBI. Further research is needed to examine whether HRQoL appears to worsen, improve or show a relatively stable trajectory into young adulthood. Further studies are also needed to evaluate the prognostic value of HRQoL measures collected earlier during the post-injury recovery and whether these measures may interact with other injury and non-injury factors to predict later HRQoL outcomes.

Despite these limitations, our study addresses several important gaps in the existing literature. Specifically, in addressing the dearth of prospective childhood TBI research by using a multidimensional subjective well-being conceptualisation of HRQoL, we identify several modifiable risk factors that can be addressed with interventions that could potentially optimise HRQoL in the very long term post-injury.

4.5. Clinical implications

Overall, our findings suggest that a substantial proportion of young adult survivors of TBI experience poor HRQoL in at least one core domain, the poorest outcomes associated with more severe depression symptoms, greater perceived communication difficulty, and reduced cognitive flexibility. These results underscore the importance of routine screening for mood and social communication difficulties in individuals with a history of TBI. For clinicians, these domains should be routinely screened with a view to initiating targeted referrals for treatment and management of these risk factors that may contribute to and maintain poor HRQoL. Encouragingly, for TBI patients with these risk factors, our findings suggest that successful intervention in these domains (e.g., cognitive behavioural therapy-based interventions for mood or social skills training for perceived communication difficulty) could optimise very-long-term HRQoL in this vulnerable population. Early evidence for the benefits of such interventions in the TBI population has been recently documented [45].

Moreover, given the elevated rates of perceived social communication difficulty at 15 years post-injury, further research is needed to determine whether speech and language deficits,

including pragmatics, may underlie these perceived difficulties. From a clinical standpoint, for patients reporting subjective communication complaints in the long term post-injury, speech and language assessment and therapy (if relevant) may be beneficial for optimizing quality of life.

5. Conclusions

To our knowledge, this is the longest running prospective study to evaluate HRQoL outcomes and their correlates in young adult survivors of childhood TBI. Our findings show that at 15 years post-injury, a substantial proportion of childhood TBI survivors experience poor HRQoL in at least 1 of 4 core functional domains. Moreover, HRQoL impairments were equally common across the spectrum of severity, and the poorest HRQoL outcomes were associated with more severe depression symptoms, greater perceived social communication difficulty, and reduced cognitive flexibility at 15 years post-injury. These findings suggest that even in the long term post-injury, the identification and treatment of modifiable risk factors has potential to improve very-long-term HRQoL outcomes in this vulnerable population.

Ethical Statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Funding

This work was supported by a grant from the Victoria Q3 Neurotrauma Initiative (CO6E1), Australia; the Victorian Government Operational Infrastructure Support Program; an Australian Postgraduate Award, MCRI PhD scholarship, and NHMRC Moving Ahead Centre for Research Excellence in Brain Injury Recovery Seed Grant to NR; and an NHMRC Senior Practitioner Fellowship to VA. The funding bodies did not play a role in the design of the study, collection, analysis and interpretation of the data, or writing of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors acknowledge the support received from Dr Senem Eren.

References

- [1] Mitra B, Cameron P, Butt W. Population-based study of paediatric head injury. *J Paediatr Child Health* 2007;43:154–9.
- [2] Crowe L, Babl F, Anderson V, Catroppa C. The epidemiology of paediatric head injuries: data from a referral centre in Victoria, Australia. *J Paediatr Child Health* 2009;45:346–50.
- [3] Anderson V, Brown S, Newitt H, Holle H. Educational, Vocational, Psychosocial, and Quality-of-Life Outcomes for Adult Survivors of Childhood Traumatic Brain Injury. *J Head Trauma Rehabil* 2009;24:303–12.
- [4] Anderson V, Brown S, Newitt H, Hoile H. Long-Term Outcome From Childhood Traumatic Brain Injury: Intellectual Ability, Personality, and Quality of Life. *Neuropsychology* 2011;25:176–84.
- [5] Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *J Neurotrauma* 2012;29:1717–27.
- [6] Polinder S, Haagsma JA, van Klaveren D, Steyerberg EW, Van Beeck E. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. *Population Health Metrics* 2015;13:4.

- [7] W.H.O.. Introduction, Administration, Scoring and Generic Version of the Assessment–Field Trial Version. Geneva, Switzerland: World Health Organization; 1996.
- [8] Limond J, Dorris L, McMillan TM. Quality of life in children with acquired brain injury: Parent perspectives 1–5 years after injury. *Brain Inj* 2009;23:617–22.
- [9] Ryan NP, Catroppa C, Cooper JM, et al. The emergence of age-dependent social cognitive deficits after generalized insult to the developing brain: a longitudinal prospective analysis using susceptibility-weighted imaging. *Hum Brain Mapp* 2015;36:1677–91.
- [10] Sesma HW, Slomine BS, Ding R, McCarthy ML. Executive functioning in the first year after pediatric traumatic brain injury. *Pediatrics* 2008;121:1686–95.
- [11] Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J. Recovery of intellectual ability following traumatic brain injury in childhood: Impact of injury severity and age at injury. *Pediatr Neurosurg* 2000;32:282–90.
- [12] Yeates KO, Bigler ED, Dennis M, et al. Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. *Psychol Bull* 2007;133:535–56.
- [13] Turkstra LS, McDonald S, DePompei R. Social information processing in adolescents: Data from normally developing adolescents and preliminary data from their peers with traumatic brain injury. *J Head Trauma Rehabil* 2001;16:469–83.
- [14] Ryan NP, Catroppa C, Beare R, et al. Theory of mind mediates the prospective relationship between abnormal social brain network morphology and chronic behavior problems after pediatric traumatic brain injury. *Soc Cogn Affect Neurosci* 2016;11:683–92.
- [15] Ryan NP, Catroppa C, Beare R, et al. Predictors of longitudinal outcome and recovery of pragmatic language and its relation to externalizing behaviour after pediatric traumatic brain injury. *Brain Lang* 2015;142:86–95.
- [16] Ryan NP, Anderson V, Godfrey C, et al. Social communication mediates the relationship between emotion perception and externalizing behaviors in young adult survivors of pediatric traumatic brain injury (TBI). *Int J Dev Neurosci* 2013;31:811–9.
- [17] Farrington DP. Juvenile delinquency. In: Coleman J, editor. *The School Years Vol 2*. London: Routledge; 1992. p. 123–63.
- [18] Schwartz L, Taylor HG, Drotar D, Stancin T, Yeates KO, Wade SL. Long-term behavior problems following pediatric traumatic brain injury: Prevalence, predictors, and correlates. *J Pediatr Psychol* 2003;28:251–63.
- [19] Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974;304:81–4.
- [20] Sparrow S, Balla D, Cicchetti DV. *Vineland Adaptive Behavior Scales-Interview Edition Survey Form Manual*. Circle Pines, Minnesota: American Guidance Service; 1984.
- [21] Noller P, Seth-Smith M, Bouma R, Schweitzer R. Parent and adolescent perceptions of family functioning: A comparison of clinic and non-clinic families. *J Adolesc* 1992;15:101–14.
- [22] Daniel AE. Power, privilege and prestige: Occupations in Australia. Cheshire: Longman; 1983.
- [23] Delis DC, Kaplan E, Kramer JH. *Delis–Kaplan Executive Function System: Examiners Manual*. New York: Psychological Corporation; 2001.
- [24] Douglas JM, O’Flaherty C, Snow PC. Measuring perception of communicative ability: The development and evaluation of the La Trobe communication questionnaire. *Aphasiology* 2000;14:251–68.
- [25] Jackson C. The General Health Questionnaire. *Occup Med* 2007;57:79–87.
- [26] Hawthorne G, Herrman H, Murphy B. Interpreting the WHOQOL-BREF: Preliminary population norms and effect sizes. *Social Indicators Research* 2006;77:37–59.
- [27] Skevington SM, Sartorius N, Amir M. Developing methods for assessing quality of life in different cultural settings. *Soc Psychiatry Psychiatr Epidemiol* 2004;39:1–8.
- [28] W.H.O.. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med* 1998;28:551–8.
- [29] Anderson VA, Catroppa C, Rosenfeld J, Haritou F, Morse SA. Recovery of memory function following traumatic brain injury in pre-school children. *Brain Inj* 2000;14:679–92.
- [30] Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. *JAMA* 2003;289:1813–9.
- [31] Felder-Puig R, Baumgartner M, Topf R, Gadner H, Formann AK. Health-related quality of life in Austrian elementary school children. *Med Care* 2008;46:432–9.
- [32] Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™ 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;3:329–41.
- [33] Fuentes MM, Wang J, Haarbauer-Krupa J, et al. Unmet rehabilitation needs after hospitalization for traumatic brain injury. *Pediatrics* 2018;141:e20172859.
- [34] Zonfrillo MR, Durbin DR, Winston FK, Zhao H, Stineman MG. Physical disability after injury-related inpatient rehabilitation in children. *Pediatrics* 2013;131:206–13.
- [35] Anderson V, Godfrey C, Rosenfeld JV, Catroppa C. Predictors of cognitive function and recovery 10 years after traumatic brain injury in young children. *Pediatrics* 2012;129:254–61.
- [36] Rosema S, Crowe L, Anderson V. Social function in children and adolescents after traumatic brain injury: a systematic review 1989–2011. *J Neurotrauma* 2012;29:1277–91.
- [37] Babikian T, Asarnow R. Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature. *Neuropsychology* 2009;23:283–96.
- [38] Li L, Liu J. The effect of pediatric traumatic brain injury on behavioral outcomes: a systematic review. *Dev Med Child Neurol* 2013;55:37–45.
- [39] Ryan NP, Hughes N, Godfrey C, Rosema S, Catroppa C, Anderson VA. Prevalence and predictors of externalizing behavior in young adult survivors of pediatric traumatic brain injury. *J Head Trauma Rehabil* 2015;30:75–85.
- [40] Krasny-Pacini A, Chevignard M, Lancien S, et al. Executive function after severe childhood traumatic brain injury–Age-at-injury vulnerability periods: The TGE prospective longitudinal study. *Ann Phys Rehabil Med* 2017;60:74–82.
- [41] Dajani DR, Uddin LQ. Review: Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends Neurosci* 2015;38:571–8.
- [42] Davis JC, Liu-Ambrose T, Marra CA, Najafzadeh M. The independent contribution of executive functions to health related quality of life in older women. *BMC Geriatr* 2010;10.
- [43] Yang Z, Oathes D, Satterthwaite TD, et al. Cognitive behavioral therapy is associated with enhanced cognitive control network activity in major depression and posttraumatic stress disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018;3:311–9.
- [44] Anderson V, Brown S, Newitt H. What contributes to quality of life in adult survivors of childhood traumatic brain injury? *J Neurotrauma* 2010;27:863–70.
- [45] Ponsford J, Wong D, McKay A, et al. Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychol Med* 2016;46:1079–90.
- [46] Câmara-Costa H, Bull KS, Kennedy C, et al. Quality of survival and cognitive performance in children treated for medulloblastoma in the PNET 4 randomized controlled trial. *Neuro-oncology practice* 2017;4:161–70.
- [47] Pullens MJ, De Vries J, Roukema JA. Subjective cognitive dysfunction in breast cancer patients: a systematic review. *Psycho-oncology* 2010;19:1127–38.
- [48] Biglia N, Bounous V, Malabaila A, et al. Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care (Engl)* 2012;21:485–92.
- [49] Zeltzer LK, Lu Q, Leisenring W, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev* 2008;17:435–46.
- [50] Scholten AC, Haagsma JA, Andriessen T, et al. Health-related quality of life after mild, moderate and severe traumatic brain injury: patterns and predictors of suboptimal functioning during the first year after injury. *Injury* 2015;46:616–24.
- [51] Arrington-Sanders R, Michael SY, Tsevat J, Wilmott RW, Mrus JM, Britto MT. Gender differences in health-related quality of life of adolescents with cystic fibrosis. *Health Qual Life Outcomes* 2006;4:5–11.
- [52] Corrigan JD, Bogner J, Harrison-Felix C, Terrill MS, Whiteneck G, Dijkers M. Systematic bias in traumatic brain injury outcome studies because of loss to follow-up. *Arch Phys Med Rehabil* 2003;84:153–60.
- [53] Babikian T, Satz P, Zaucha K, Light R, Lewis RS, Asarnow RF. The UCLA longitudinal study of neurocognitive outcomes following mild pediatric traumatic brain injury. *J Int Neuropsychol Soc* 2011;17:886–95.
- [54] Kirkwood MW, Yeates KO, Taylor HG, Randolph C, McCrema M, Anderson VA. Management of pediatric mild traumatic brain injury: A neuropsychological review from injury through recovery. *The Clinical Neuropsychologist* 2008;22:769–800.
- [55] Maillard-Wermelinger A, Yeates KO, Gerry Taylor H, et al. Mild traumatic brain injury and executive functions in school-aged children. *Developmental neurorehabilitation* 2009;12:330–41.
- [56] Rohling ML, Larrabee GJ, Millis SR. The “Miserable Minority” following mild traumatic brain injury: Who are they and do meta-analyses hide them? *The Clinical Neuropsychologist* 2012;26:197–213.
- [57] Chesnel C, Jourdan C, Ruet A, et al. Self-awareness four years after severe traumatic brain injury: discordance between the patient’s and relative’s complaints. Results from the Paris-TBI study. *Clin Rehabil* 2018;32:692–704.