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**Self- and Parent-reported Quality of Life Seven Years after Severe Childhood Traumatic Brain Injury in the Traumatisme Grave de l'Enfant cohort: Associations with Objective and Subjective Factors and Outcomes**

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**Disclosure of interest**

The authors have no competing interest to report.

**Abstract**

**Purpose:** To investigate self- and parent-reported Health-Related Quality-of-Life (HRQoL) and their associations after severe childhood traumatic brain injury (TBI) in the Traumatisme Grave de l'Enfant (TGE) cohort.

**Methods:** Self- (n=34) and/or parent-reports (n=25) of HRQoL were collected for 38 participants (age 7-22 years) seven years after severe childhood TBI. The collected data included socio-demographic characteristics, injury severity indices, and overall disability and functional outcome at 3-months, 1- and 2-years post-injury. At 7-years post-injury, data was collected in the TBI group and in a control group (n=33): overall disability (Glasgow Outcome Scale Extended), intellectual ability (IQ), and questionnaires assessing HRQoL (Pediatric Quality of Life Inventory), executive functions (Behavior Rating Inventory of Executive Functions), Behavior (Child Behavior Checklist), fatigue (Multidimensional Fatigue Scale) and participation (Child and Adolescent Scale of Participation).

**Results:** Parent- and self-reports of HRQoL were significantly lower in the TBI group than in the control group. Parent-rated HRQoL was not associated with objectively assessed factors; whereas self-reported HRQoL was associated with gender (worse in females) and initial functional outcome. All questionnaire scores completed by the same informant (self or parent) were strongly inter-correlated.

**Conclusions:** Reported HRQoL 7-years after severe childhood TBI is low compared to controls, weakly or not-related to objective factors, such as injury severity indices, clinically assessed functional outcomes, or IQ, but strongly related to reports by the same informant of executive deficits, behavior problems, fatigue, and participation.

**Keywords:** Severe traumatic brain injury, child, adolescent, health-related quality of life, prospective cohort study

**Self- and Parent-reported Quality of Life Seven Years after Severe Childhood Traumatic Brain Injury in the Traumatisme Grave de l'Enfant cohort: Associations with Objective and Subjective Factors and Outcomes**

Quality of life (QoL), as defined by the WHO [1], is a subjective construct, based on personal perceptions, expectations, standards and beliefs. Thus assessment of a person's QoL must be performed by asking this person. This definition might appear excessively subjective and static (i.e. lacking prospect) to medical doctors. In some cases, medical interventions might be required in subjects reporting excellent QoL according to the WHO.

Severe pediatric Traumatic Brain Injury (TBI) reaches 3% to 7% of overall pediatric TBI incidence, estimated to fall between 47 and 280 per 100,000 children [2], and is among the most prominent causes of child mortality and long-term disability in developed countries [3, 4]. The detrimental impact of childhood TBI on long-term cognitive, social and educational outcomes has been consistently reported [5–9].

The pertinence of investigating Health-Related Quality of Life (HRQoL) following childhood TBI has been highlighted [10, 11], since poorer reports of HRQoL tend to persist into adulthood [12], especially after severe TBI [13], although severity is not systematically associated with worse reports of HRQoL [12]. HRQoL is a multi-dimensional construct describing an individual's satisfaction and subjective well-being across several functional domains, such as physical, social, cognitive or emotional functioning. Children and adolescents with TBI report lower HRQoL than comparison groups [14–16]. Socio-demographic and injury-related factors can negatively impact HRQoL following childhood TBI, such as lower parental socio-economic status [17] and post-injury cognitive, behavioral and social difficulties [12, 18]. Reported findings regarding the relationship between HRQoL post-TBI and age at injury are conflicting [19, 20]. Low HRQoL and greater fatigue levels have been associated with greater injury severity [21, 22], although previous studies included small numbers of patients with severe TBI.

The present prospective longitudinal study included exclusively participants with severe TBI followed 7-years post-injury, and a closely matched control group. The primary aim of the study was to investigate self- and parent-reports of HRQoL 7-years post-injury, compared to those of the control group. Secondary aims were to study factors associated with HRQoL, taking into account the multidimensional nature of this construct. Among factors potentially associated with HRQoL, a clear distinction was made between “objective” assessments (e.g., socio-demographic factors, injury severity indices, clinical and neuropsychological assessments) and “subjective” questionnaire-based measures (assessing various constructs), in order to compare the strength of

their respective associations with HRQoL. For the primary aim, we hypothesized that participants who underwent severe TBI would evidence lower self- and parent-reported HRQoL, when compared to controls. As for the secondary aim, we hypothesized that self and parents' reports of HRQoL would be more strongly associated with subjective questionnaire-based measures, when compared to objective assessments.

## **METHODS**

The TGE study (*Traumatisme Grave de l'Enfant* [TGE] - severe childhood trauma) is a prospective longitudinal investigation of children aged under 16 years consecutively admitted within the 6 hours following severe accidental TBI to the intensive care unit (ICU) of the Necker Enfants Malades Hospital between January 2005 and December 2008 [24, 25]. Severe TBI was defined as a Glasgow Coma Scale (GCS) score  $\leq 8$  [26] upon admission and/or an Injury Severity Score (ISS)  $> 16$  [27].

Eighty-one children were enrolled at the acute stage of TBI. Exclusion criteria included: no vital signs upon admission, non-accidental head injury, and previous history of diagnosed neurological, psychiatric or learning disorders. Sixteen children died in acute care, leaving 65 children eligible for follow-up, which comprised: comprehensive medical, functional and neuropsychological assessment at 3-months, 1-, 2- and 7-years post-injury. All eligible patients received treatment according to international guidelines for the management of severe TBI [28] in the neurosurgical Intensive Care Unit (ICU) of the Necker Enfants Malades regional pediatric trauma center. A large majority (83%) required/received multidisciplinary rehabilitation after acute care in the Rehabilitation Department for Children with Acquired Neurological Injury (Saint Maurice Hospitals). At the 7-year post-injury follow-up, the study design included a group of closely matched healthy controls.

### **Participants**

#### ***Patients with severe TBI***

From the 65 eligible participants, 38 (59%) were available for the 7-year follow-up. Main reasons for attrition were patients having moved and being lost to follow-up, declining participation to the follow-up study, or unavailable data on the HRQoL questionnaire 7-years post-injury, which was mainly due to failure to return (or refusal of answering) the questionnaires, and parental foreign background (unable to understand and/or speak French). Seven-years post-injury, 34 of the participants (90%) had available data on self-reports of HRQoL, 25 (66%) on parent-reports, and 21 (55%) on both self- and parent-report forms.

#### ***Controls***

Controls were recruited from local schools or via general medical practices. The exclusion criteria were those for the TBI sample, as well as presence of a history of TBI. Controls were matched to participants in the TBI group

with respect to age ( $\pm 3$  months), gender and parental education ( $\pm 2$  years' education). Thirty-three controls (87%) had available data on HRQoL: 33 self-reports; 20 both self- and parent-reports.

### **Measures**

Table 1 presents all the variables measured and the assessment tools used in the present study.

[INSERT TABLE 1 HERE]

### ***Participants with TBI***

#### ***Socio-demographic characteristics***

We collected data on children's age at assessment, gender and family background at the time of the 7-year follow-up. Parental education was dichotomized into medium-high (at least one parent had a secondary school diploma ["baccalauréat"]) or low (neither parent had a secondary school diploma). For family situation, we generated a dichotomous variable defining if the child was living with both biological parents or not (non-marital or monoparental status), and family size was defined as the number of siblings living in the household. Pre-injury education status was defined into two levels according to parental reports: the child exhibited academic difficulties and/or required extra help at school and/or had stayed back one year versus absence of school difficulties or extra help or grade retention.

#### ***Injury severity***

During the acute phase in the ICU, we collected information on age at injury, mean length of coma (in days) and cause of accidental TBI (motor vehicle accidents and falls). Trauma severity was assessed using three measures: the Glasgow Coma Scale (GCS) [26], the Pediatric Trauma Score (PTS) [29], and the Injury Severity Score (ISS) [27, 30].

#### ***Post-TBI outcome measures at 3-months, 1-year and 2-years post-injury***

The *Pediatric Injury Functional Outcome Scale* (PIFOS), used in children aged 3 to 15 years, aims to assess functional outcome [31] using 26 items (scored 0 [no change from pre-injury levels] to 4 [increasing need for support and limitations to daily activities]), and a total score, higher PIFOS scores reflecting greater difficulties.

The *Glasgow Outcome Scale* modified for children [32] classifies overall disability into 5 categories: good outcome, moderate disability, severe disability, vegetative state, and death.

#### ***Outcome measures 7-years post-injury***

***Post-TBI outcome:*** We used the GOS-Extended Pediatric (GOS-E Peds) [33] and Adult version (GOS-E) [32], yielding 8 categories of overall disability, among which good recovery, moderate disability and severe disability (upper or lower levels), vegetative state, and death.

**Motor deficits:** Clinician-rated assessment for absence or presence of cerebellar dysfunction (ataxia and/or coordination disorders) and/or hemiplegia or hemiparesis.

**Ongoing education (TBI and control groups):** Self or parental information on current education status was dichotomized into either mainstream education (enrollment in general education classrooms, with or without help) or special education (attendance of specialized institutions, or special education classrooms in regular schools).

**Intellectual ability** was assessed using age-appropriate Wechsler scales (ages  $\leq 16$  years - Wechsler Intelligence Scale for Children-IV [34]; ages  $>16$  years - Wechsler Adult Intelligence Scale-IV [35]), yielding a Verbal Comprehension Index (VCI), a Perceptive Reasoning Index (PRI), a Working Memory Index (WMI), a Processing Speed Index (PSI), and a Full-Scale Intellectual Quotient (FSIQ), (Mean=100, SD=15 for all measures).

**HRQoL** was assessed using French-validated adaptations of the Pediatric Quality of Life Inventory (PedsQL) [36]. Age-appropriate versions of self-report (participants aged  $\geq 5$  years) and parent-report forms were used. PedsQL yields four Generic Core Scales: Physical health (8 items), Emotional Functioning (5 items), Social Functioning (5 items), School Functioning (5 items); two Summary Scores: Physical Health (8 items) and Psychosocial Health (15 remaining items); and a total HRQoL Score (all 23 items). The scores are expressed in a 0 to 100-scale with higher scores indicating better HRQoL.

**Executive functioning** was evaluated with the Behavior Rating Inventory of Executive Functions (BRIEF) [37, 38]. Age-appropriate self- and parent-report forms allow to calculate a Global Executive Composite (GEC) T-score (Mean=50, SD=10). Higher GEC scores reflect worse executive functioning.

**Behavioral problems** were assessed with the Achenbach's Behavior Checklist [39, 40]. Age-appropriate versions of self- and parent-reports were used: Children's Behavior Checklist (ages 4-18 years), Youth Self-Report (ages 11-18 years), Adult Behavior Checklist and Adult Self-report (ages  $>18$  years). Higher total T-scores (Mean=50, SD=10) indicate increased behavior problems.

**Fatigue** was evaluated with the age-appropriate self- and parent-reports of the Multidimensional Fatigue Scale (MFS) [41]. Total fatigue scores are converted in a 0 to 100 scale with higher scores reflecting lower levels of fatigue.

**Participation** was examined with the self- and parent-reports of the Child and Adolescent Scale of Participation (CASP) [42, 43]. Higher summary scores (0 to 100-point scale) indicate higher levels of participation.



**Procedure**

Parents of children and adult participants provided written informed consent to participate in the study, which was approved by the *Comité de Protection de Personnes d'Île-de-France VI* [CPP IDF VI] ethics committee. Patients and/or parents (for patients under 18 years) included in the initial stages of the TGE study were contacted and were offered to participate in the 7-year follow-up. Participants who agreed to take part in the follow-up were then invited to perform two assessment sessions in the Saint Maurice Hospital. One session was conducted by a specialized physician, who collected data on current education and occupation, medication, degree of care needs, and ongoing rehabilitation therapy; performed a neurological examination screening for motor, visual or hearing impairments; and administered the GOS-E or GOS-E Peds. The second session, performed on a different day (with recesses), was conducted by a trained neuropsychologist who carried out the neuropsychological assessments and handled the self-report questionnaires, while parents responded to the questionnaires separately. In some cases, the psychologist helped participants and/or their parents to complete the questionnaires, whenever they evidenced insufficient reading, comprehension and/or cognitive skills to understand the questions.

The procedures for collecting data in the control group were the same as for the TBI group, except that they were not subjected to the medical examination and were given a reduced set of neuropsychological tests.

**Statistical Analyses**

Data analyses were performed using SAS© software version 9 [44]. In a first set of analyses, we conducted univariate analyses (Wilcoxon signed-rank test, Fisher Exact test) for group comparisons between participants with TBI and controls according to sociodemographic characteristics and for all outcome measures (questionnaires and performance-based assessments) collected at the 7-year follow-up. Additionally, we used repeated measures analysis of variance (Generalized Linear Model) to examine the evolution of functional outcome and overall disability at 3-months, 1-, 2- and 7-years postinjury in the group of participants with TBI. Intraclass correlation procedures (Shrout-Fleiss reliability coefficient for fixed effects) were also used to investigate the associations between self- and parent-reports of HRQoL.

For the second set of analyses, we focused on the group of participants who underwent severe TBI to investigate the factors (sociodemographic, initial injury severity, overall disability and functional outcome within the first 2-years post-injury, and 7-year post-injury concurrent outcome measures) associated with HRQoL scores.

Univariate analyses were followed by linear regression procedures with self- and parent-reported HRQoL as the

dependent variable. Statistical significance was two-tailed and set at  $p < .01$ , also considering  $p < .05$  as marginally significant.

## RESULTS

Preliminary analyses indicated no significant differences between patients who participated in the 7-year follow-up study ( $n=38$ ) and non-participants ( $n=27$ ) on socio-demographic characteristics (age at injury, parental education, family situation and size), initial injury severity (GCS, ISS, PTS, and length of coma), and 3-months, 1- and 2-years post-TBI outcomes (overall disability, functional outcome, FSIQ and BRIEF scores;  $p > 0.05$  in all cases).

Reliability indices of internal consistency for the HRQoL total scores were good both for patients with severe TBI (Cronbach alpha: self-reports,  $\alpha=.78$ ; parent-reports,  $\alpha=.78$ ) and for controls (self-reports,  $\alpha=.71$ ; parent-reports,  $\alpha=.83$ ), justifying the computation of a total HRQoL score, in addition to the four generic core scales and the Psychosocial Health score (sum of the Emotional, Social, and School/Work scales) of the PedsQL [45]. Table 2 describes the main characteristics of the 38 participants of the TBI group. All participants sustained initial coma (GCS score  $\leq 8$ ) with mean length of coma of 6.6 days. A repeated measures ANOVA with the PIFOS score as the dependent variable and time (3-months, 1- and 2-years post-injury) as explanatory variable showed an overall decrease of the PIFOS score ( $F(2,58)=3.56$ ,  $p=.03$ ). The mean PIFOS total score (functional outcome) decreased significantly (less impairment) between 3-months and 1-year post-TBI ( $F(1,29)=6.77$ ,  $p=.015$ ), but remained comparable between 1- and 2-years ( $p=.68$ ). The same analyses were performed using the GOS score as the dependent variable and time (3-months, 1-, 2- and 7-years post-injury) as explanatory variable indicated an overall decrease of the GOS score disability with time ( $F(3,111)=13.77$ ,  $p < .0001$ ). The proportion of participants with severe disability tended to decrease between 3-months and 2-years post-injury (42% vs. 26%), and the proportion of those with good recovery tended to increase (from 8% to 19%) ( $F(1,37)=5.03$ ,  $p=.003$ ). At 7-years post-injury, overall disability was severe for 8 participants (21%), moderate for 9 (24%), and 21 (55%) had good recovery, showing significant improvement in overall disability compared to the 2-year post-injury status ( $F(1,37)=16.33$ ,  $p=.0003$ ). Motor deficits were reported in 7 (18%) participants.

[INSERT TABLE 2 HERE]

### **Group comparisons between participants with severe TBI and controls at the 7-year follow-up (Table 3)**

**Parent-reported HRQoL:** Compared to controls, participants with TBI exhibited significantly lower Total, Psychosocial Health and Social functioning scores.

**Self-reported HRQoL:** With the exception of the Emotional functioning scale, participants who underwent TBI reported significantly lower HRQoL than controls on the Total score and the Physical Health, Psychosocial Health, Social Functioning and School/Work functioning scales.

[INSERT TABLE 3 HERE]

**Ongoing education and intellectual ability (Table 4):** Seven-years post-injury, all 33 controls were enrolled in regular classrooms, in comparison with 30 (79% of 38) of the participants with TBI. Mean FSIQ was significantly lower in the TBI group compared to controls, yet presented considerable variability.

**Concurrent outcomes: executive functions, behavior, fatigue, and participation (Table 4)**

**Parent-reports:** Compared to controls, parents of patients who underwent severe TBI reported significantly more impairments on executive functioning, more behavioral problems, higher levels of fatigue and lower levels of participation.

**Self-reports:** Participants with TBI reported significantly more behavior problems and higher fatigue levels when compared to controls. Self-reports of executive functioning and participation were not significantly different between groups.

[INSERT TABLE 4 HERE]

### **Correlations between parent-reported and self-reported HRQoL**

The intraclass correlations between the same HRQoL scales completed by parents and patients were moderate for the HRQoL Total score ( $r=.56, p=.009$ ), Physical Health ( $r=.66, p=.001$ ), Psychosocial Health ( $r=.50, p=.02$ ), Social ( $r=.59, p=.005$ ) and School/Work functioning scales ( $r=.64, p=.002$ ), but low for Emotional Functioning ( $r=.18, p=.44$ ). In the control group, the parent-self intraclass correlations were low ( $r$  range =.20 to .37,  $p>.05$ ), except for school/working ( $r=.45, p=.04, n=20$ ).

### **Factors associated with HRQoL in the TBI group 7-years post-injury**

#### **Socio-demographic factors, injury severity indices, and clinical and neuropsychological assessments between 3-months and 7-years post-TBI (Table 5)**

**Parent-reported HRQoL:** There was no significant link of the HRQoL total score with age or age at injury, gender, parental education, family situation and size, initial injury severity indices, functional outcome (PIFOS) and disability categories (GOS-Peds) at 3 months, 1-year and 2-years post injury.

At 7-years post-injury, the parent-reported HRQoL Total score was not associated to overall disability, motor impairments, ongoing education or IQ indices. Only the School/Work functioning score was moderately correlated with FSIQ ( $r=.41, p=.048$ ) and VIQ ( $r=.44, p=.03$ ).

**Self-reported HRQoL:** Lower HRQoL total score was associated with female gender ( $p=.009$ ), poorer functional outcomes (PIFOS) at 3-months ( $p=.008$ ), 1-year ( $p=.004$ ) and 2-years post-injury ( $p=.0003$ ), and with increased disability (GOS-Peds) 1-year ( $p=.008$ ) and 2-years post-injury ( $p=.03$ ). Among the four HRQoL scales, female gender was significantly linked to lower Physical Health ( $p=.01$ ) and Emotional functioning ( $p=.005$ ) scores. Physical Health was associated with initial injury severity (GCS score,  $r=.35$ ,  $p=.045$ ), and with all PIFOS and GOS/GOS-E scores at 3-months, 1-year, 2-years and 7-years post-injury ( $r$  -.38 to -.63,  $p<.05$  in all cases). Social and School/work functioning correlated moderately with some PIFOS and GOS-Peds scores at 3-months, 1-year or 2-years post injury ( $r$  -.37 to -.43,  $p<.05$  in all cases). Self-reported HRQoL was associated neither with age at injury nor with family background (parental education, family situation and size). Seven-years post-injury, the self-reported HRQoL Total score was associated neither to overall disability or presence of motor impairments, nor to ongoing education or IQ indices. Increased overall disability (GOS-E) 7-years post-TBI was associated with poorer HRQoL in the Physical Health ( $r=-.44$ ,  $p=.01$ ) and School/Work functioning scales ( $r=-.39$ ,  $p=.02$ ). Increased HRQoL in the School/Work functioning scale score was also moderately associated with higher (better) scores in the Working Memory Index ( $r=.36$ ,  $p=.04$ ).

[INSERT TABLE 5 HERE]

#### **Questionnaire-based outcomes (Table 6)**

**Parent-reports:** All the correlations of the HRQoL total score with the remaining parent-rated questionnaires (executive functions, behavior, fatigue and participation) were significant ( $r$  ranging from .52 for participation to .80 for fatigue). Correlation coefficients of each of the four HRQoL scales with the remaining parent-rated questionnaires ranged from .36 to .78. The associations of parent-reported HRQoL with self-rated questionnaires were generally weaker in magnitude, but significant for self-rated fatigue and participation.

**Self-reports:** The HRQoL Total score was significantly associated with all self-ratings of executive functioning, behavior, fatigue and participation ( $r$  ranging from .57 for behavior and participation to .75 for fatigue). Correlation coefficients between each of the four HRQoL scales and other self-rated questionnaires ranged from .37 to .71. Correlations between self-reported HRQoL total score and parent-rated questionnaires were significant for participation, fatigue and behavior, and non-significant for executive functioning.

[INSERT TABLE 6 HERE]

#### **Multivariate analyses: associations of HRQoL with objective and subjective factors**

The parent-reported total score was significantly associated with parent-reported fatigue ( $p=.02$ ) and behavioral problems ( $p=.04$ ), when controlling for the effects of the remaining variables. None of the sociodemographic,

initial injury severity, clinical and neuropsychological assessments were significantly associated with parent-reports of HRQoL.

The self-reported total score was significantly associated with gender ( $p=.04$ ) and overall disability 1-year post-injury ( $p=.02$ ). However, when the self-reported questionnaires were entered in the regression model, only self-reported fatigue ( $p=.03$ ) remained significantly associated with self-reported HRQoL, while the effects of gender and overall disability were no longer significant.

## DISCUSSION

In the present prospective longitudinal study, participants who were followed over a 7-year period after severe childhood TBI and their parents reported reduced HRQoL compared to matched controls. All domains of HRQoL scored lower in patients with TBI than in controls. This observation aligns well with previous reports indicating that following TBI, patients are more likely to experience poor HRQoL than healthy controls [14, 16] or reference populations [12, 18, 45–47]. Mean proxy and self-report scores of HRQoL were similar. Agreement between self and proxy-report was fairly good, except for the emotional functioning domain, as previously reported [48, 49].

Self-reported (but not parent-reported) HRQoL 7-years post-injury was associated with earlier functional outcomes, from 3-months to 2-years post-injury, in accordance with a previous meta-analysis indicating that assessments conducted 1-year post-injury are amongst the most significant predictors of HRQoL [10]. However, it is unclear why long term (7-years post injury) self-reported HRQoL is more strongly associated with earlier functional outcomes than parent-reported HRQoL. As this prospective study shows, the proportion of patients with “good recovery” GOS outcomes increased strongly at 7-years post-injury, compared to earlier assessments. Possibly, self-reported long-term HRQoL is more influenced by memory of past difficulties during the early post-TBI period, than parent-reported long-term HRQoL. Clinically assessed disability at 7-years post-injury (GOS) correlated moderately ( $r=.39$ ) with the HRQoL Physical Health scale only, both in parent- and self-reports, which makes sense and is compatible with previous findings [50, 51].

Female gender was associated with lower self-reported HRQoL, especially in the domains of physical health and emotional functioning, unlike a recent study performed 15-years after childhood mild to severe TBI [12].

However our results are in accordance with previous studies performed in other pediatric acquired brain injury conditions, such as brain tumors [52]. There seems to be little empirical evidence on gender differences in HRQoL following childhood TBI, although the prognostic significance of gender on recovery after childhood TBI has been recently highlighted in the case of moderate TBI [53]. Contrary to previous findings, in the present

study age at injury, parental education and family situation were not associated with reports of HRQoL [17, 19]. Verbal Comprehension Index and Working memory indices of the Wechsler scales showed moderate correlations with the School/Work PedsQL functioning scale, which could be related to the influence of those important cognitive functions on academic performance, and thus the feeling of achievement and well-being in a school environment.

In accordance with previous reports, the present study evidenced that participants who underwent severe TBI reported increased difficulties in the questionnaires assessing executive functioning [15], behavioral problems [54], fatigue [55] and participation [56], when compared to the control group, except for self-reported executive functioning and self-reported participation. Intellectual ability was also significantly lower in the group of participants with TBI, compared to controls [7]. However, the high variability observed in the intellectual performance of participants after severe TBI should be highlighted, with some patients performing well below average, while others were functioning at higher levels.

Overall, socio-demographic factors, injury severity indices, and clinical and neuropsychological assessments explained a very small part of the variance of parent-reported HRQoL and a small part of the variance of self-reported HRQoL 7-years post-TBI. In contrast, questionnaires completed by the same informant explained a very large part of the variance of reported HRQoL. When the effects of the different questionnaires on HRQoL reports were taken into account in the regression models, no other factor remained significant. Why are such strong correlations found between questionnaires developed to assess distinct constructs? One may consider that all these questionnaires evaluate constructs that can be components of quality of life and, as a consequence, strong correlations between them would be expected. This assumption seems reasonable, especially for fatigue and participation. According to other sources [57, 58], the wording of all the items of the questionnaires used in the present study, had a positive/negative polarity, which could in itself also generate strong inter-correlations between questionnaires. There is general consensus that it is better to answer “never” rather than “always” at questions such as “feeling afraid or scared” (PedsQL), “does not check work for mistakes” (BRIEF), “teases a lot” (CBCL), “feels tired” (MFS), and an “age expected” answer is better rather than an “unable” answer at “communicating with other children and adults at school” (CASP). When the same person completes these questionnaires, personal factors (anxiety, mood, personality), contextual factors (why I am asked this question? Is it better for me to give overall negative or positive answers?), response shift [59] or being emotionally upset [60] could all contribute to some extent to generate or strengthen correlations. Given that anxiety, mood or

personality were not assessed in the respondents in this study, this question cannot be answered based on this study alone.

Some limitations should be taken into account when interpreting the results of the present study. The sample size of the TBI and the control groups was slightly different, and therefore our analyses were performed in a group level basis rather than at an individually-matched level. The small sample sizes might have contributed to hinder some correlations and associations, in addition to the presence of missing data in some assessments (e.g. self-reported BRIEF) and the relatively broad age range. However, in comparison to previous studies using heterogeneous samples (mild, moderate and severe TBI), the present sample size constitutes a rather considerable group of participants since they refer exclusively to children and adolescents who underwent a severe TBI and were prospectively followed-up over 7 years. Indeed, the results observed in the present study are consistent with previous research and add to the existing literature pertaining to the factors associated to HRQoL following severe pediatric TBI, highlighting the weak associations with objective assessments and the strong associations with subjective questionnaire-based measures.

In conclusion, 7-years after severe childhood TBI, reported HRQoL is lower than in controls, it is moderately influenced by objective factors and strongly linked to other reported difficulties regarding executive functions, behavior, fatigue or participation. Investigations of associations with HRQoL should clearly separate subjective factors collected by questionnaires or interviews from socio-demographic, clinical, neuropsychological or other more objectively assessed factors. This important outcome should, however, be assessed and considered more systematically during long-term follow-up after severe childhood brain injury. Factors negatively influencing HRQoL could be identified and adequate interventions implemented for those patients when possible, based not only on their self- and (when available) proxy-reports, but also on their overall medical, neuropsychological, emotional, and environmental situation. Future studies should ensure that special attention is also given to concurrent assessment of anxiety, mood and personality when assessing HRQoL, as some of those aspects could be accessible to targeted interventions, that in turn could allow improvement of overall wellbeing and satisfaction [12].

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**Table 1.** List of the variables measured and the assessment tools used in the Traumatisme Grave de l'Enfant (TGE) cohort

| Sociodemographic characteristics | Initial Injury Severity         | Post-Severe Traumatic Brain Injury outcomes |                                         |                                         |                                                 |
|----------------------------------|---------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------------------|-------------------------------------------------|
|                                  |                                 | 3-months                                    | 1-year                                  | 2-years                                 | 7-years                                         |
| Age at follow-up                 |                                 |                                             |                                         |                                         |                                                 |
| Gender                           |                                 |                                             |                                         |                                         |                                                 |
| Parental education level         |                                 |                                             |                                         |                                         |                                                 |
| Family situation                 |                                 |                                             |                                         |                                         |                                                 |
| Family size                      |                                 |                                             |                                         |                                         |                                                 |
| Pre-injury education             |                                 |                                             |                                         |                                         |                                                 |
|                                  | <b>Clinician-rated measures</b> |                                             |                                         |                                         |                                                 |
|                                  | Age at injury                   |                                             |                                         |                                         |                                                 |
|                                  | GCS                             |                                             |                                         |                                         |                                                 |
|                                  | PTS                             |                                             |                                         |                                         |                                                 |
|                                  | ISS                             |                                             |                                         |                                         |                                                 |
|                                  | Length of coma                  |                                             |                                         |                                         |                                                 |
|                                  |                                 | Functional outcome<br>. <i>PIFOS</i>        | Functional outcome<br>. <i>PIFOS</i>    | Functional outcome<br>. <i>PIFOS</i>    |                                                 |
|                                  |                                 | Overall disability<br>. <i>GOS Peds</i>     | Overall disability<br>. <i>GOS Peds</i> | Overall disability<br>. <i>GOS Peds</i> | Overall disability<br>. <i>GOS-E/GOS-E Peds</i> |
|                                  |                                 |                                             |                                         |                                         | Motor deficits                                  |
|                                  |                                 |                                             |                                         |                                         | <b>Performance-based measures</b>               |
|                                  |                                 |                                             |                                         |                                         | Ongoing education                               |
|                                  |                                 |                                             |                                         |                                         | Intellectual Ability ( <i>Wechsler scales</i> ) |
|                                  |                                 |                                             |                                         |                                         | . Full Scale Intellectual Quotient              |
|                                  |                                 |                                             |                                         |                                         | . Verbal Comprehension Index                    |
|                                  |                                 |                                             |                                         |                                         | . Perceptual Reasoning Index                    |
|                                  |                                 |                                             |                                         |                                         | . Working Memory Index                          |
|                                  |                                 |                                             |                                         |                                         | . Processing Speed Index                        |
|                                  |                                 |                                             |                                         |                                         | <b>Questionnaire-based measures</b>             |
|                                  |                                 |                                             |                                         |                                         | Health-Related Quality of Life                  |
|                                  |                                 |                                             |                                         |                                         | . <i>PedsQL</i>                                 |
|                                  |                                 |                                             |                                         |                                         | Executive Functioning                           |
|                                  |                                 |                                             |                                         |                                         | . <i>BRIEF/BRIEF-A</i>                          |
|                                  |                                 |                                             |                                         |                                         | Behavioral problems                             |
|                                  |                                 |                                             |                                         |                                         | . <i>CBCL/YSR/ABCL/ASR</i>                      |
|                                  |                                 |                                             |                                         |                                         | Fatigue                                         |
|                                  |                                 |                                             |                                         |                                         | . <i>MFS</i>                                    |
|                                  |                                 |                                             |                                         |                                         | Participation                                   |
|                                  |                                 |                                             |                                         |                                         | . <i>CASP</i>                                   |

GCS: Glasgow Coma Scale; PTS: Paediatric Trauma Score; ISS: Injury Severity Score; PIFOS: Pediatric Injury Functional Outcome; GOS Peds: Pediatric Glasgow Outcome Scale; GOS-E/GOS-E Peds: Glasgow Outcome Scale-Extended; Glasgow Outcome Scale-Extended, Pediatric version; PedsQL: Pediatric Quality of Life Inventory; BRIEF: Behavior Rating Inventory of Executive Function; BRIEF-A: BRIEF Adult version; CBCL: Child Behavior Checklist; YSR: Youth Self-Report; ABCL: Adult Behavior Checklist; ASR: Adult Self-Report; MFS: Multidimensional Fatigue Scale; CASP: Child and Adolescent Scale of Participation.

**Table 2.** Descriptive statistics of the study participants: baseline sociodemographic characteristics, initial TBI severity, overall disability and functional outcome from 3-months to 2-years post-TBI, and overall disability, motor deficits and performance-based assessments 7-years post-injury.

|                                                              | <b>Severe TBI (n = 38)</b>        |
|--------------------------------------------------------------|-----------------------------------|
|                                                              | <b>Mean (SD) [Range] or n (%)</b> |
| <b>Sociodemographic characteristics</b>                      |                                   |
| Age at follow-up                                             | 15.3 (4.5) [7.4 - 22.7]           |
| Gender (male)                                                | 24 (63)                           |
| Parental education level (medium-high <sup>a</sup> )         | 19 (50)                           |
| Family situation (child living with both biological parents) | 26 (68)                           |
| Family size (number of children in the household)            | 3.7 (1.4) [1 - 6]                 |
| Pre-injury education (assisted and/or Delayed)               | 5 (13)                            |
| <b>Initial Injury Severity</b>                               |                                   |
| Age at injury (years)                                        | 7.5 (4.6) [.3 - 14.7]             |
| Lowest Glasgow Coma Scale Score                              | 5.8 (1.7) [3 - 8]                 |
| Paediatric Trauma Score                                      | 3.9 (2.3) [-1 - +9]               |
| Injury Severity Score                                        | 27.5 (9.7) [4 - 50]               |
| Length of coma (days)                                        | 6.6 (4.9) [1 - 22]                |
| <b>3-months post-TBI outcomes</b>                            |                                   |
| Functional outcome (PIFOS score)                             | 1.2 (0.7) [0.08 - 2.9]            |
| Overall disability (GOS Peds), n (%)                         |                                   |
| <i>Good Recovery</i>                                         | 3 (8)                             |
| <i>Moderate Disability</i>                                   | 19 (50)                           |
| <i>Severe Disability</i>                                     | 16 (42)                           |
| <b>1-year post-TBI outcomes</b>                              |                                   |
| Functional outcome (PIFOS score)                             | 1.03 (0.6) [0.2 - 2.8]            |
| Overall disability (GOS Peds), n (%)                         |                                   |
| <i>Good Recovery</i>                                         | 5 (13)                            |
| <i>Moderate Disability</i>                                   | 21 (55)                           |
| <i>Severe Disability</i>                                     | 12 (32)                           |
| <b>2-years post-TBI outcomes</b>                             |                                   |
| Functional outcome (PIFOS score)                             | 1.08 (0.7) [0.08 - 2.9]           |
| Overall disability (GOS Peds), n (%)                         |                                   |
| <i>Good Recovery</i>                                         | 7 (19)                            |
| <i>Moderate Disability</i>                                   | 21 (55)                           |
| <i>Severe Disability</i>                                     | 10 (26)                           |
| <b>7-years post-TBI outcomes</b>                             |                                   |
| Overall disability (GOS-E/GOS-E Peds), n (%)                 |                                   |
| <i>Good Recovery</i>                                         | 21 (55)                           |
| <i>Moderate Disability</i>                                   | 9 (24)                            |
| <i>Severe Disability</i>                                     | 8 (21)                            |
| Motor deficits, n (%)                                        |                                   |
| <i>Presence</i>                                              | 7 (18)                            |
| <b>Performance-based measures</b>                            |                                   |
| Ongoing education, n (%) <sup>††</sup>                       |                                   |
| <i>Specialized</i>                                           | 8 (21)                            |
| Intellectual ability (FSIQ)                                  | 86.3 (18.3) [40 - 129]            |

TBI: Traumatic Brain Injury; SD: Standard Deviation; GOS Peds: Pediatric Glasgow Outcome Scale; GOS-E/GOS-E Peds: Glasgow Outcome Scale-Extended; Glasgow Outcome Scale-Extended, Pediatric version; PIFOS: Pediatric Injury Functional Outcome; FSIQ: Full Scale Intellectual Quotient; a: At least one of the parents had a high school diploma.

**Table 3.** Group comparisons of parent- and self-report mean scores on the Pediatric Quality of Life Inventory between participants 7-years post severe TBI and controls

|                                            | Severe TBI |      |      | Controls |      |      | <i>t</i> | <i>p</i> <sup>†</sup> |
|--------------------------------------------|------------|------|------|----------|------|------|----------|-----------------------|
|                                            | N          | Mean | SD   | N        | Mean | SD   |          |                       |
| <b>Pediatric Quality of Life Inventory</b> |            |      |      |          |      |      |          |                       |
| <i>Parent-reports</i>                      |            |      |      |          |      |      |          |                       |
| Total score                                | 25         | 71.7 | 18.9 | 20       | 83   | 17   | 2.09     | .029                  |
| Physical health                            | 25         | 72.4 | 27.2 | 20       | 83.1 | 23.2 | 1.40     | .110                  |
| Psychosocial health                        | 25         | 71.3 | 16.9 | 20       | 83.1 | 14.4 | 2.49     | .020                  |
| Emotional functioning                      | 25         | 68   | 22.1 | 20       | 79.8 | 14.9 | 2.03     | .079                  |
| Social functioning                         | 25         | 74.4 | 21.8 | 20       | 90   | 18.1 | 2.57     | .012                  |
| School/Work functioning                    | 25         | 70.2 | 20.5 | 20       | 79.5 | 22.2 | 1.46     | .140                  |
| <i>Self-reports</i>                        |            |      |      |          |      |      |          |                       |
| Total score                                | 34         | 71.2 | 18.3 | 33       | 83.9 | 12.7 | 3.32     | .002                  |
| Physical health                            | 34         | 75.8 | 22.2 | 33       | 88.8 | 17.6 | 2.66     | .002                  |
| Psychosocial health                        | 34         | 68.8 | 19.5 | 33       | 81.3 | 13.5 | 3.04     | .010                  |
| Emotional functioning                      | 34         | 63.7 | 25.3 | 33       | 71.8 | 22.7 | 1.38     | .208                  |
| Social functioning                         | 34         | 76.9 | 24.4 | 33       | 90.3 | 13.3 | 2.78     | .013                  |
| School/Work functioning                    | 34         | 63.8 | 23.9 | 33       | 80.9 | 15.5 | 3.46     | .002                  |

<sup>†</sup> Two-tailed Wilcoxon signed-rank test; TBI: Traumatic Brain Injury; SD: Standard deviation.

**Table 4.** Group comparisons between patients with TBI and controls according to performance- and questionnaire-based measures collected at the 7-years follow-up

|                                     | Severe TBI<br>( <i>n</i> = 38) |                           | Controls<br>( <i>n</i> = 33) |                           | <i>p</i> <sup>†</sup> |
|-------------------------------------|--------------------------------|---------------------------|------------------------------|---------------------------|-----------------------|
|                                     | N                              | Mean (SD) [Range]         | N                            | Mean (SD) [Range]         |                       |
| <b>7-years follow-up outcomes</b>   |                                |                           |                              |                           |                       |
| <b>Performance-based measures</b>   |                                |                           |                              |                           |                       |
| Ongoing education, <i>n</i> (%)     | 38                             |                           | 33                           |                           |                       |
| <i>Mainstream</i>                   |                                | 30 (79)                   |                              | 33 (100)                  | .006 <sup>††</sup>    |
| Intellectual ability (FSIQ)         | 35                             | 86.3 (18.3) [40 - 129]    | 33                           | 98.9 (13.4) [63 - 124]    | .0008                 |
| <b>Questionnaire-based measures</b> |                                |                           |                              |                           |                       |
| <b><i>Parent-reports</i></b>        |                                |                           |                              |                           |                       |
| Executive Function                  |                                |                           |                              |                           |                       |
| <i>BRIEF GEC</i>                    | 30                             | 60.3 (14.8) [37 - 89]     | 27                           | 50.2 (14.8) [37 - 73]     | .008                  |
| Behavior                            |                                |                           |                              |                           |                       |
| <i>CBCL/ABCL Total score</i>        | 33                             | 59.3 (10.4) [39 - 78]     | 30                           | 50.9 (8.8) [25 - 69]      | .002                  |
| Fatigue                             |                                |                           |                              |                           |                       |
| <i>MFS Total score</i>              | 25                             | 67.8 (20.3) [31.9 - 100]  | 20                           | 87.6 (11.4) [58.3 - 100]  | .0006                 |
| Participation                       |                                |                           |                              |                           |                       |
| <i>CASP Total score</i>             | 37                             | 86.4 (14.8) [31.7 - 100]  | 31                           | 96.4 (4.8) [82.5 - 100]   | .0004                 |
| <b><i>Self-reports</i></b>          |                                |                           |                              |                           |                       |
| Executive Function                  |                                |                           |                              |                           |                       |
| <i>BRIEF-A GEC</i>                  | 12                             | 61.4 (10.8) [46 - 79]     | 12                           | 53.5 (11.6) [40 - 71]     | .088                  |
| Behavior                            |                                |                           |                              |                           |                       |
| <i>YSR/ASR Total score</i>          | 24                             | 58.4 (10.4) [35 - 75]     | 24                           | 51.8 (7.4) [37 - 67]      | .014                  |
| Fatigue                             |                                |                           |                              |                           |                       |
| <i>MFS Total score</i>              | 34                             | 61.1 (18.8) [27.8 - 94.4] | 33                           | 77.4 (15.3) [41.7 - 97.2] | .0006                 |
| Participation                       |                                |                           |                              |                           |                       |
| <i>CASP Total score</i>             | 27                             | 89.1 (10.6) [62.5 - 100]  | 26                           | 91.2 (9.6) [66.3 - 100]   | .44                   |

<sup>†</sup> Two-tailed Wilcoxon signed-rank test; <sup>††</sup> Fisher Exact two-sided chi-square test; M: Mean; SD: Standard deviation; FSIQ: Full Scale Intellectual Quotient; BRIEF: Behavior Rating Inventory of Executive Functions; GEC: Global Executive Composite; CBCL: Child Behavior Checklist; ABCL: Adult Behavior Checklist; MFS: Multidimensional Fatigue Scale; CASP: Child and Adolescent Scale of Participation, BRIEF-A: BRIEF Adult version; YSR: Youth Self-Report; ASR: Adult Self-Report.

**Table 5.** Associations of parent- and self-reported Health-Related Quality of Life in the TBI group with baseline socio-demographic characteristics, initial TBI severity, overall disability and functional outcome from 3-months to 2-years post-TBI, and overall disability, motor deficits and performance-based assessments 7-years post-injury.

|                                         | Pediatric Quality of Life Inventory |          |          |             |          |          |
|-----------------------------------------|-------------------------------------|----------|----------|-------------|----------|----------|
|                                         | Parent-report                       |          |          | Self-report |          |          |
|                                         | Total score                         |          |          | Total score |          |          |
|                                         | <i>n</i>                            | <i>r</i> | <i>p</i> | <i>n</i>    | <i>r</i> | <i>p</i> |
| <b>Sociodemographic characteristics</b> |                                     |          |          |             |          |          |
| Age at assessment                       | 25                                  | -.14     | .518     | 34          | -.001    | .995     |
| Gender <sup>†</sup> (es)                | 25                                  |          | .734     | 34          | (.92)    | .009     |
| Parental educational level <sup>†</sup> | 25                                  |          | .723     | 34          |          | .890     |
| Family situation <sup>†</sup>           |                                     |          | .708     |             |          | .883     |
| Family size                             | 25                                  | -.12     | .582     | 34          | -.20     | .249     |
| Pre-injury education <sup>†</sup>       | 25                                  |          | .098     | 34          |          | .285     |
| <b>Initial Injury Severity</b>          |                                     |          |          |             |          |          |
| Age at injury                           | 25                                  | -.19     | .357     | 34          | -.08     | .665     |
| Lowest GCS Score                        | 25                                  | .12      | .570     | 34          | .15      | .394     |
| Pediatric Trauma Score                  | 25                                  | -.27     | .196     | 34          | .0001    | .999     |
| Injury Severity Score                   | 25                                  | -.14     | .499     | 34          | -.18     | .300     |
| Length of coma                          | 25                                  | -.007    | .973     | 34          | -.26     | .131     |
| <b>3-months post-TBI</b>                |                                     |          |          |             |          |          |
| PIFOS                                   | 18                                  | -.14     | .593     | 29          | -.48     | .008     |
| GOS Peds                                | 25                                  | -.14     | .502     | 34          | -.29     | .100     |
| <b>1-year post-TBI</b>                  |                                     |          |          |             |          |          |
| PIFOS                                   | 19                                  | -.19     | .441     | 30          | -.51     | .004     |
| GOS Peds                                | 25                                  | -.13     | .527     | 34          | -.45     | .008     |
| <b>2-years post-TBI</b>                 |                                     |          |          |             |          |          |
| PIFOS                                   | 20                                  | -.26     | .278     | 31          | -.61     | .0003    |
| GOS Peds                                | 25                                  | -.27     | .197     | 34          | -.37     | .031     |
| <b>7-years post-TBI</b>                 |                                     |          |          |             |          |          |
| GOS-E/GOS-E Peds                        | 25                                  | -.36     | .079     | 34          | -.26     | .141     |
| Motor deficits <sup>†</sup>             | 25                                  |          | .919     | 34          |          | .456     |
| Performance-based measures              |                                     |          |          |             |          |          |
| Ongoing education <sup>†</sup>          | 25                                  |          | .275     | 34          |          | .789     |
| Intellectual ability                    |                                     |          |          |             |          |          |
| <i>FSIQ</i>                             | 24                                  | .09      | .661     | 32          | .07      | .706     |
| <i>VCI</i>                              | 24                                  | .10      | .639     | 33          | -.009    | .959     |
| <i>PRI</i>                              | 24                                  | -.06     | .794     | 33          | -.06     | .731     |
| <i>WMI</i>                              | 24                                  | .12      | .573     | 33          | .29      | .104     |
| <i>PSI</i>                              | 24                                  | .08      | .693     | 32          | .10      | .578     |

<sup>†</sup> Two-tailed Wilcoxon signed-rank test (*Z*); es: effect size (Cohen's *d*); All other associations were examined using Pearson correlation procedures (*r*); GCS: Glasgow Coma Scale; PIFOS: Pediatric Injury Functional Outcome; GOS Peds: Pediatric Glasgow Outcome Scale; GOS-E/GOS-E Peds: Glasgow Outcome Scale-Extended; Glasgow Outcome Scale-Extended, Pediatric version; FSIQ: Full Scale Intellectual Quotient; VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index.



**Table 6.** Associations of parent- and self-reported Health-Related Quality of Life in the TBI group with questionnaire-based measures collected at the 7-year follow-up.

|                                     | Pediatric Quality of Life Inventory |          |          |             |          |          |
|-------------------------------------|-------------------------------------|----------|----------|-------------|----------|----------|
|                                     | Parent-report                       |          |          | Self-report |          |          |
|                                     | Total score                         |          |          | Total score |          |          |
|                                     | <i>n</i>                            | <i>r</i> | <i>p</i> | <i>n</i>    | <i>r</i> | <i>p</i> |
| <b>7-years post-TBI</b>             |                                     |          |          |             |          |          |
| <b>Questionnaire-based measures</b> |                                     |          |          |             |          |          |
| <b>Parent-reports</b>               |                                     |          |          |             |          |          |
| Executive Functions                 |                                     |          |          |             |          |          |
| <i>BRIEF GEC</i>                    | 22                                  | -.61     | .003     | 27          | -.22     | .27      |
| Behavior                            |                                     |          |          |             |          |          |
| <i>CBCL/ABCL Total score</i>        | 22                                  | -.67     | .0006    | 30          | -.43     | .02      |
| Fatigue                             |                                     |          |          |             |          |          |
| <i>MFS Total</i>                    | 25                                  | .80      | <.0001   | 21          | .52      | .02      |
| Participation                       |                                     |          |          |             |          |          |
| <i>CASP Total</i>                   | 25                                  | .52      | .0007    | 33          | .57      | .0005    |
| <b>Self-reports</b>                 |                                     |          |          |             |          |          |
| Executive Functions                 |                                     |          |          |             |          |          |
| <i>BRIEF-A GEC</i>                  | -                                   | -        | -        | 12          | -.73     | .007     |
| Behavior                            |                                     |          |          |             |          |          |
| <i>YSR/ASR Total</i>                | 12                                  | -.55     | .07      | 24          | -.57     | .003     |
| Fatigue                             |                                     |          |          |             |          |          |
| <i>MFS Total</i>                    | 21                                  | .59      | .005     | 34          | .75      | <.0001   |
| Participation                       |                                     |          |          |             |          |          |
| <i>CASP Total</i>                   | 15                                  | .55      | .03      | 27          | .57      | .002     |

*r*: Pearson correlation test; BRIEF: Behavior Rating Inventory of Executive Function; GEC: Global Executive Composite; CBCL: Child Behavior Checklist; ABCL: Adult Behavior Checklist; MFS: Multidimensional Fatigue Scale; CASP: Child and Adolescent Scale of Participation, BRIEF-A: BRIEF Adult version; YSR: Youth Self-Report; ASR: Adult Self-Report.