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Project Title: Health-Related Quality of Life in Pediatric Concussion/Mild Traumatic Brain Injury: Systematic Review and Prospective Study

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Summary: Concussion and mild traumatic brain injury (mTBI) are burgeoning topics in health research. The explosion of new information in recent years creates a need for frequent knowledge synthesis efforts to keep clinicians and researchers up-to-date. Few objective outcome measures exist for concussion/mTBI and, as such, patient-reported outcomes have become important tools for assessing recovery. One such outcome is health-related quality of life (HRQOL). We conducted a systematic review on HRQOL in pediatric mTBI/concussion as well as our own prospective study, examining HRQOL in adolescents with concussion specifically, using the Pediatric Quality of Life Inventory (PedsQL), in order to better understand the typical progression of HRQOL after these injuries. Results of the systematic review revealed that there is a small but important proportion (~12%) of pediatric mTBI patients who experience substantial diminishments in their HRQOL up to a year or longer post-injury. Predictors of poor HRQOL included older age, low SES or a history of headaches or trouble sleeping. The prospective study showed significant HRQOL differences between those who developed post-concussion syndrome (PCS) and those who did not, starting from the first post-concussion clinic visit. A cutoff score of 82.81 on the initial visit physical subscale of the PedsQL predicted those who would develop PCS with 89.5% sensitivity and 66.7% specificity, which is superior to tools previously described in the literature. HRQOL represents an important outcome measure in pediatric concussion/mTBI, with applications in both clinical practice and research. However, further study is needed to fully realize its potential utility in these areas.

Student Signature

Supervisor Signature

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INTRODUCTION

Concussion and mild traumatic brain injury:

Concussion and mild traumatic brain injury (mTBI) have emerged as important public health concerns with an estimated incidence of 600/100 000 population[1]. In the United States, the terms mTBI and concussion are often used interchangeably, and are considered equivalent by the Centers for Disease Control and Prevention[2]. The Zurich Consensus Statement on Concussion in Sport, however, states that many use the terms to refer to different injury constructs[3]. Generally, it is thought that mTBI includes both structural and functional injuries, whereas concussion is primarily a functional entity that represents a subset of mTBI[3,4].

Clinical manifestations of concussion/mTBI in pediatric patients are highly variable and include physical, cognitive, sleep and mood-related symptoms[5,6]. With conservative management and adequate levels of physical and cognitive rest, approximately 80-90% of concussed adults will experience neurological recovery within 7-10 days[3]; however, children and adolescents may take longer to recover[3,7,8,9]. Some patients will experience persistent symptoms lasting greater than 1 to 3 months and be diagnosed with post-concussion syndrome (PCS)[10]. Studies suggest that patients with PCS are at an elevated risk of developing further impairments in physical, psychological, and social functioning including chronic headaches, vestibular dysfunction, aerobic de-conditioning, mood disorders, social isolation and poor academic performance[11,12,13].

Defining health-related quality of life:

Health-related quality of life (HRQOL) is a multi-disciplinary concept that captures the effect of disease states on a patient's physical, mental and social wellbeing and has emerged as an important patient-reported outcome (PRO)[14,15]. Although quality of life and HRQOL are often used interchangeably, HRQOL refers specifically to aspects of life that are directly affected by one's health[14,15].

Measuring health-related quality of life:

Assessment of HRQOL is applicable both to acute and chronic conditions. HRQOL questionnaires can be completed by the patient or by a proxy. HRQOL measurement tools may be generic (i.e., applied to any disease or condition) or disease-specific. Generic HRQOL instruments allow for the comparison of HRQOL across multiple, unrelated diseases. Examples of generic HRQOL instruments previously used in pediatric mTBI/concussion include the PedsQL[16], the KINDL[17] and the Child Health Questionnaire[18]. Presently, there are no pediatric mTBI/concussion-specific HRQOL instruments available.

It may not be possible for the patient to report his or her own HRQOL and a proxy, usually a parent or caregiver, may have to complete the assessment. Research demonstrates that children as young as 5 years of age can reliability assess their HRQOL, while parents can provide proxy assessments of HRQOL in children as young as 2 years of age with appropriate instruments[15]. A systematic review of pediatric HRQOL studies concluded that while good agreement was observed among pediatric patients and parents for physical HRQOL domains (such as symptoms), agreement was poor for social and emotional HRQOL domains[19]. As such, the authors recommend that both patient and parental assessments of HRQOL should be obtained whenever feasible[19].

HRQOL in pediatric concussion/mTBI:

Despite accumulating evidence of impaired HRQOL among children and adolescents following any traumatic brain injury (TBI) (reviewed in Di Battista et al., 2012[20]), there is limited understanding of HRQOL in pediatric patients with mild TBI/concussion or PCS specifically. With an increase in the incidence of diagnosed mTBI/concussion[21] and greater understanding of the

potential long-term effects of mTBI/concussion[22], the field has seen an explosion of new research in recent years, and frequent knowledge synthesis efforts are needed in order to allow researchers and clinicians to stay up to date. Thus, the objectives of the current study are: 1. To summarize the current state of knowledge on HRQOL in pediatric concussion/mTBI and PCS patients through a systematic review and 2.To conduct a prospective study on HRQOL in pediatric concussion that addresses gaps in the literature.

METHODS

Systematic Review

Literature search:

A systematic search of the literature was performed by a professional health sciences librarian across the following nine databases from their earliest date of coverage through June 1, 2015: MEDLINE, PubMed, Embase (Ovid), Scopus, CINAHL (EBSCO), SPORTDiscus (EBSCO), Cochrane Central, PEDro, and Child Development & Adolescent Studies (EBSCO). While specific searches varied in keeping with the options available within each database, a combination of controlled vocabulary and keyword queries were used whenever possible. Subject headings included: brain concussion, brain injuries, pediatrics, adolescent, child, preschool, infant, infant-newborn, health status, and quality of life. The following keywords were also used to access literature that was not as well represented by the subject headings: concussion, post-concussion, TBI, traumatic brain injury, brain injury, teenager, youth, health related quality of life, and well-being. The full search strategies for each database are available from the authors upon request. Two reviewers independently reviewed the titles and abstracts to identify potentially relevant studies. If one or both reviewers deemed the citation to be potentially relevant, the full text was obtained and the inclusion criteria, detailed below, were applied.

Inclusion criteria:

The following a-priori determined inclusion criteria were applied to each potentially relevant study independently by two reviewers:

1. Studies must have examined the effects of isolated physician-diagnosed concussion or mTBI in a pediatric/adolescent population (<20 years old);
2. Studies must have measured two or more HRQOL domains (e.g. physical, cognitive, social, emotional) in the patient after concussion/mTBI using a validated HRQOL measurement tool. The HRQOL scales could have been completed by the patient, their proxy or both;
3. Studies must be primary research, excluding case reports, published in a peer-reviewed academic journal or in grey literature (e.g.; PhD Dissertation); and,
4. Studies must be available in English.

Studies that met all four inclusion criteria were included. All discrepancies between reviewers were resolved through consensus or by a third reviewer as needed. The reference lists of included studies were reviewed for any additional potentially relevant studies.

Data extraction and assessment of methodological quality:

Study data were extracted using a standardized form focusing on study design, study inclusion/exclusion criteria, recruitment method, sample size, participant characteristics, setting (inpatient versus outpatient), mTBI/concussion diagnostic criteria, cause of injury (eg. sports, motor vehicle, falls, etc.), HRQOL measurement tool, time points that HRQOL was assessed, patient versus proxy report, control groups (ie. baseline, non-injured, non-brain injured), predictors of HRQOL, statistical methods, results, conclusions, study funding and methodological quality/risk of bias, using the Scottish Intercollegiate Guidelines[23]. A second independent reviewer then verified data extraction forms for accuracy and completeness.

Data analysis:
Substantial heterogeneity in the timing of HRQOL measurements, HRQOL tools used, proxy versus child reporting, and definitions of mTBI/concussion precluded performing a meta-analysis. A descriptive analysis was instead performed and the results were summarized in a narrative fashion.

Prospective Case Series
Research ethics board approval was received from the University of Manitoba. Adolescents, aged 13-18, with isolated concussions, as diagnosed by a neurosurgeon concussion specialist, were recruited consecutively from the Pan Am Clinic Concussion Program in Winnipeg, Canada. Inclusion criteria were age 13-18, isolated physician-diagnosed concussion, and able to speak, read and write in English. If patients were deemed study-eligible at their first visit to the clinic, a research assistant or student in clinic would confirm their eligibility, explain the study and outline the patient's role in the study. If the patients and their guardians were willing to participate, the parent/guardian would sign a consent form and the adolescent would sign an assent form, as well as co-sign the consent form. Following signing the consent and assent forms, the participants completed a demographic information form.

At the first visit, and all subsequent clinic visits, the patients would complete the Pediatric Quality of Life Inventory 4.0 (PedsQL) core scale and cognitive functioning scale[16]. The PedsQL is a 23-item validated generic tool to assess HRQOL in pediatric populations[16]. The core scale includes physical, social, emotional and school domains. Versions are available for 5-7 year olds, 8-12 year olds and 13-18 year olds (the version used in this study). The scale asks patients to rank how much of a problem each item is on a Likert scale from zero to four. Examples of items on the adolescent version of the PedsQL include "It is hard for me to walk more than one block", "I feel afraid or scared", "I cannot do things that other teens my age can do" and "I miss school because of not feeling well". In addition, the six-question cognitive functioning scale from the PedsQL Multidimensional Fatigue Scale was administered to assess quality of life diminishments associated with the cognitive dysfunction that is often observed in concussion.

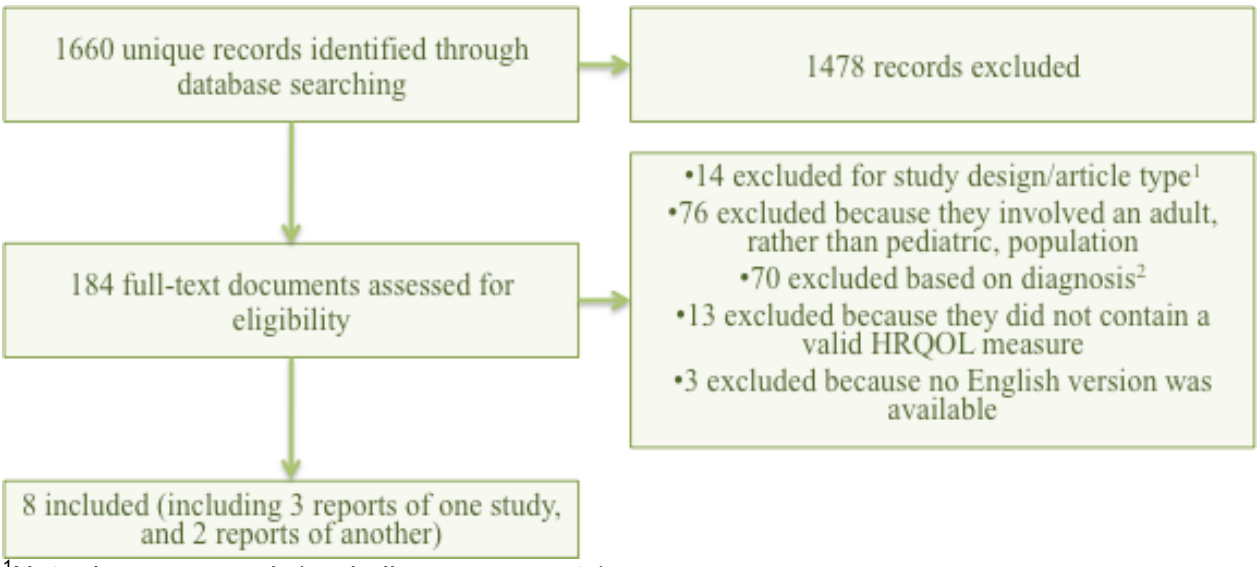
Patients were seen at the clinic until the treating neurosurgeon determined that they had recovered from their concussion. To be considered fully recovered, patients must have returned to school full time (or been able to), completed recommended protocols for return to sport if appropriate, and must have recovered from any vestibulo-ocular dysfunction associated with their concussion. If symptoms persisted greater than one month, the patient was diagnosed with PCS using the ICD-10 criteria[24].

Data Analysis:
Data was analyzed both by visit number and by number of weeks post-injury. Number of visits to recovery was tabulated. For each HRQOL domain, means were calculated across each time point. Student's T testing was used to compare the mean initial visit PedsQL scores in each domain between those who developed PCS and those who did not (based on ICD-10 criteria[24]). Generalized estimating equations modeling was conducted to determine mean change with 95% confidence intervals (out of 100 points) in HRQOL score over each week while accounting for repeated measures within each patient. Initial visit PedsQL scores in each domain for those who developed PCS and those who did not were also used to construct receiver operating characteristic (ROC) curves. This method allows for the selection of cutoff values to differentiate between the two groups based on desired balance between sensitivity and specificity.

RESULTS

Systematic Review

The search results are outlined in Figure 1. Eight manuscripts, representing five unique studies were included (Table 1, Appendix). One study was identified as a PhD dissertation and as two journal articles (with one reporting additional time points)[25,26,27]. Two of the studies were also conducted amongst the same group of patients, with different data analyses performed in each[28,29]. Reviewing the reference lists of the included manuscripts did not yield any additional studies.



[1]Not primary research (excluding case reports)
[2]Not isolated mTBI/concussion

Figure 1: PRISMA flow diagram outlining the search process and results.

Description of included studies:

The studies were published between 2008 and 2014. Three were completed in the United States[25,26,27,28,29,30], one in Germany[31], and one in Australia[32]. Ages of participants ranged from 2 to 17 years, with all studies including both children (12 years and younger) and adolescents (13 years or older)[25,26,27,28,29,30,31,32]. All studies used the term mTBI, none focused exclusively on concussion[25,26,27,28,29,30,31,32]. Only one of the five studies compared mTBI patients to uninjured controls[25,26,27], while two of the studies compared mTBI patients to patients with mild non-brain injuries[25,26,27,28,29,]. The total number of unique participants with mTBI included in analyses across all studies was 733[25,26,27,28,29,30,31,32].

The PedsQL[25,26,27,30] and CHQ[28,29,32] were each utilized in two studies. One study used the KINDL questionnaire[31]. A description of the different HRQOL measurement tools can be found in Table 2. Four studies used proxy reports exclusively to measure HRQOL in at least some of the children/adolescents[28,29,30,31]. Only one study used both proxy and child-completed HRQOL measures for all participants[25,26,27]. Four of the studies asked participants to retrospectively complete HRQOL evaluations to assess their preinjury/baseline status[25,26,27,28,29,30,32].The timing of HRQOL measurements was variable: one study assessed HRQOL at first contact post-injury[31], one assessed HRQOL at one month post injury[25,26,27], three assessed it at three months post-injury[27,28,29,30], one at three months after first contact[31], two at six months post injury[27,32] and three assessed HRQOL at 12 months post-injury[27,28,29,30].

Table 2: Description of HRQOL measurement tools used by included studies

HRQOL Measurement Tool	Domains Assessed	Score Range
Pediatric Quality of Life Inventory (PedsQL)[16]	Core: • Physical • Emotional • Social • School +/- Additional Scales: • eg. Cognitive Functioning	0 (worst possible health measured by the PedsQL) to 100 (best possible health measured by the PedsQL)
Child Health Questionnaire (CHQ)[18,33]	• Physical • Psychosocial	0 (worst possible health measured by the CHQ) to 100 (best possible health measured by the CHQ)
KINDL[17]	• Mental • Physical • Everyday Life • Social Life	0 (worst possible health measured by the KINDL) to 100 (best possible health measured by the KINDL)

Proportion of pediatric mTBI patients with poor HRQOL outcomes:
Only one study attempted to quantify the proportion of patients who had poor HRQOL outcomes[30]. Zonfrillo and colleagues found that 11.3% of mTBI patients reported a decrease in their PedsQL scores of 15 or more between baseline and 3 months post-injury and 12.9% reported a decrease of 15 or more points between baseline and 12 months after injury[30]. The authors used a cutoff of 15 points on the PedsQL as it represents the approximate difference between the mean score for healthy children and those with moderately severe chronic health conditions[30,34,35].

Predictors of poor HRQOL outcomes following mTBI:
Three studies aimed to identify predictors of poor HRQOL in youth after mTBI[28,29,30,31]. Zonfrillo and colleagues found that poor HRQOL was significantly associated with older age, Hispanic ethnicity, less parental education, Medicaid insurance (versus private insurance), lower levels of household income (in a gradated fashion: <30,000; <60,000; <100,000; >100,000 USD), and a history of headaches or trouble sleeping[30]. Poor HRQOL was defined as a 15 point or more reduction in PedsQL score from baseline. Additionally, a significant correlation was found between poor HRQOL scores and poor results on the Strengths and Difficulties Questionnaire (a behavioural screening questionnaire) and the revised Functional Status II questionnaire (a measurement of self-care, mobility and other functional capabilities) using Spearman or Pearson coefficients ($p<.001$ for both questionnaires at first contact post-injury and 3 months later)[31,36,37]. Greater somatic post-concussion symptoms were associated with worse physical HRQOL at both 3 and 12 months post-injury ($p=.008$) and greater somatic and cognitive symptoms were associated with worse psychosocial HRQOL ($p=.004$ for cognitive symptoms, $p=.035$ for somatic symptoms)[28]. Similarly, increases in both physical and cognitive symptoms at 3 months post-injury (but not one or the other independently) were associated with diminished physical HRQOL at that time point (mean difference: 17.43; 95% CI: 10.37–24.49) but not at 12 months post-injury[29]. Increases in cognitive symptoms at 3 months post-injury were associated with worse psychosocial HRQOL at both 3 and 12 months (3 months, mean difference: 6.27; 95% CI: 2.72–9.82; 12 months, mean difference: 8.36; 95%CI: 4.54–12.18)[29]. Symptom increases were in turn more likely in mTBI youth who experienced a loss of consciousness at the time of injury and in youth with abnormalities indicated on magnetic resonance imaging[29].

Comparing mTBI to uninjured controls:
Only one small study reported comparisons between youth with mTBI and uninjured controls[25,26,27]. They did not find any significant differences in PedsQL scores between the mTBI patients and uninjured controls at any time point[25,26,27].

Comparing mTBI to controls with mild non-brain injury:
One study reported worse HRQOL outcomes on the PedsQL from mild non-brain injury youth at 1 month post-injury compared with mTBI youth (p=.009 for child reports, p=0.002 for parent reports)[25,26,27]. The non-brain injuries were defined as children with non-operative injuries such as closed fractures, sprains, dislocations, lacerations, bruises, or burns. However, Moran and colleagues reported significantly worse physical HRQOL on the CHQ in mTBI youth at 12 months post-injury compared with patients with orthopedic injuries[28]. Between 1 and 12 months post-injury, the physical HRQOL of children with orthopedic injuries had improved, while that of the mTBI patients remained largely unchanged. In this study, orthopedic injury was defined as an upper or lower extremity fracture yielding a score of 1 to 3 on the Abbreviated Injury Scale, excluding those who had evidence of head trauma or symptoms of concussion[38].

Variance in child versus proxy reports:
One study that used collateral reporting from both patient and proxy found a significant difference between the two reports. The children reported lower HRQOL than their proxies estimated in all areas except cognitive functioning[25,26].

Prospective Case Series
62 patients met eligibility criteria and were recruited into the study. 48.4% of patients in the study developed PCS. The median number of visits before recovery was 4 (mean 3.8).

The PedsQL data was analyzed both by visit number and by weeks post-injury. Data from the school subscale were excluded due to the fact that a large portion of this study was conducted over the summer, when most patients were not in school. This led to confusion about how to complete this section; some patients left it blank, while others completed the section imagining what things would be like if they had been in school. As a result, these results could not be interpreted reliably.

Patients reported low HRQOL on the physical, emotional and cognitive functioning scales at the first visit, which all then steadily improved until the 3rd-4th visit, at which point they plateaued (Table 3, Figure 2). This was the point at which most patients were medically cleared and discharged from the clinic. The most prominent deficits in these initial visits were in the physical and cognitive functioning domains. The average HRQOL of the remaining patients declined precipitously from the 5th to 8th visit. These are the patients who developed long-lasting post-concussion syndrome. Notably, while the cognitive effects remained prominent in these patients, the impact on the emotional and social quality of life domains became more pronounced than the physical effects as time went on.

Table 3: Mean PedsQL score in each domain for each follow-up clinic visit

Visit	Mean Physical Score (n)	Mean Emotional Score (n)	Mean Social Score (n)	Mean Cognitive Functioning Score (n)
1	65.78 (40)	78.31 (62)	91.71 (59)	59.68 (62)
2	80.72 (47)	85.25 (61)	92.42 (60)	72.61 (61)
3	88.25 (45)	87.25 (51)	94.51 (51)	75.08 (50)
4	88.96 (32)	87.43 (35)	93.43 (35)	74.17 (35)
5	90.03 (19)	83.68 (19)	90.79 (19)	74.12 (19)
6	85.31 (10)	76.82 (11)	85.00 (11)	64.77 (11)
7	80.63 (5)	61.00 (5)	69.00 (5)	57.50 (5)
8	64.84 (4)	48.75 (4)	54.75 (4)	48.75 (4)

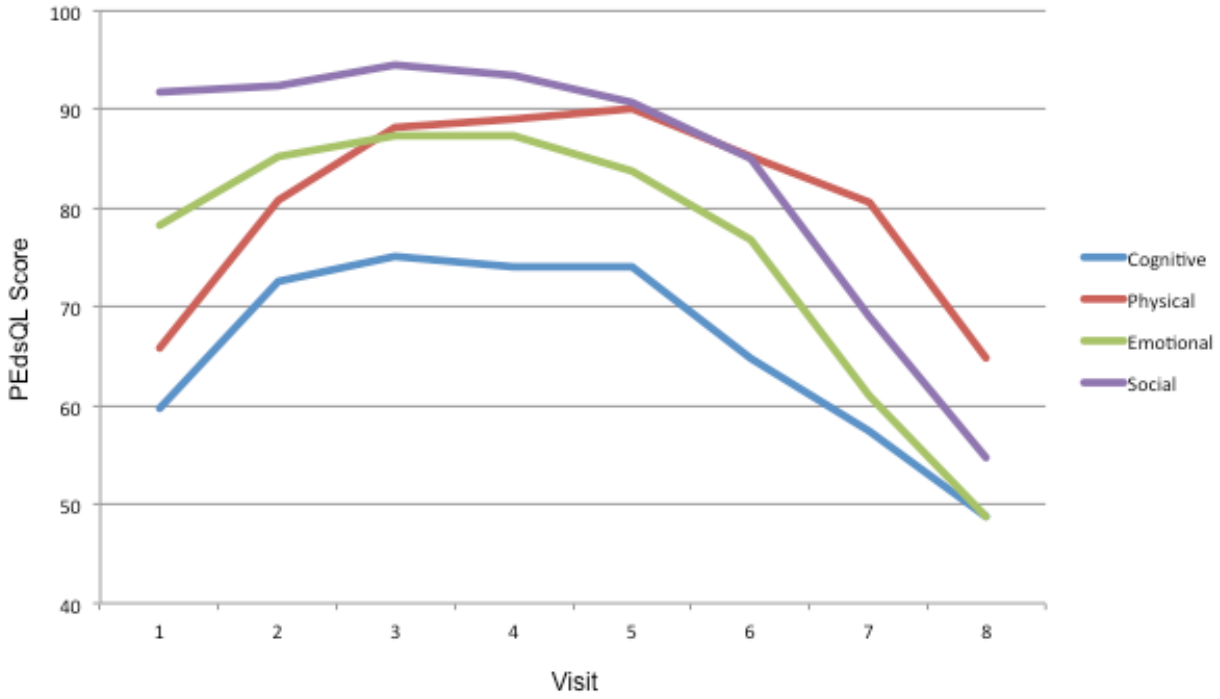


Figure 2: Mean PedsQL score in each domain across follow-up clinic visits

Analyzing the data by weeks post-injury revealed statistically significant improvements each week in all HRQOL domains except the social domain. The average week-to-week improvement for each domain can be found in Table 4. The mean week-to-week improvement in the cognitive functioning and social domains also differed significantly between those who developed PCS and those who did not. These results can be found in Table 5.

Table 4: Mean week-to-week improvement from initial follow-up visit to recovery in each PedsQL domain

PedsQL domain	Mean week-to-week improvement	95% confidence interval	P-value
Physical	2.45	1.86-3.03	<0.0005*
Emotional	1.26	0.84-1.68	<0.0005*
Social	0.15	-0.17-0.46	0.353
Cognitive Functioning	1.94	1.28-2.60	<0.0005*

*Statistically significant at p<0.05

Table 5: Comparison of mean week-to-week improvement from initial follow-up visit to recovery in each PedsQL domain between those who developed PCS and those who did not

PedsQL domain	Mean week-to-week improvement –no PCS	95% confidence interval	Mean week-to-week improvement – PCS	95% confidence interval
Physical	4.46	2.11-6.81	2.68	2.05-3.31
Emotional	2.59	0.77-4.41	1.31	0.87-1.75
Social	1.98	0.56-3.40	0.14	-0.19-0.46
Cognitive Functioning	9.22	6.66-11.77	1.87	1.18-2.56

The average initial visit PedsQL score was also significantly different between those who went on to develop PCS and those who did not, in all domains except the social domain (Table 6). Of all the PedQL subscales, the initial visit physical subscale score showed the greatest difference between those who did and did not develop PCS (p=0.0001). Receiver operating characteristic curve analysis revealed that a sensitivity of 0.895 and a specificity of 0.667 for developing PCS could be achieved using a cutoff score of 82.81 on the PedsQL physical subscale at the initial visit. This low threshold cutoff (high sensitivity, moderate specificity) was selected in order to minimize the risk of missing cases who will go on to develop PCS.

Table 6: Comparison of initial follow-up mean PedsQL score in each domain between those who developed PCS and those who did not

PedsQL domain	Mean initial visit score – no PCS	95% confidence interval	Mean initial visit score - PCS	95% confidence interval	P-value
Physical	80.8	70.36-91.25	49.2	38.19-60.16	0.0001*
Emotional	85.9	79.32-92.55	70.2	63.33-77.00	0.0015*
Social	91.7	86.55-96.89	87.2	81.60-92.85	0.24
Cognitive Functioning	67.8	59.40-76.28	51.0	42.25-59.69	0.0073*

*Statistically significant at p<0.05

DISCUSSION

Systematic Review

While the majority of patients with mTBI experience a complete recovery in a relatively short period of time, there is a small but notable minority who experience prolonged effects[9,39]. The studies identified in this review confirm that this is also reflected in HRQOL outcomes. Early

identification of the subgroup of pediatric mTBI patients who experience poor HRQOL is important so that these outcomes can be mediated as much as possible. Predictors identified in this review include older age, high ratings of post-concussion symptoms, as well as increases in symptoms. Clinicians can use HRQOL measurement tools to assess high-risk patients in order to ensure that they receive adequate management and follow-up care. By repeatedly measuring HRQOL during the recovery phase, clinicians will be able to monitor improving or declining HRQOL, which may be a global representation of the mTBI recovery process.

Several studies also found that some mTBI patients have compromised HRQOL up to 1 year or longer post-injury. This prolonged recovery may have implications on academic performance or psychosocial wellbeing, such as social isolation and increased risk of developing adverse psychiatric outcomes[40]. In addition, schools may have to provide academic accommodations to ensure these children are able to successfully attend school and complete their work. These potential impacts of prolonged recovery warrant further investigation.

Another important finding identified was a difference between child and proxy reports, where children reported lower HRQOL than their proxies estimated in all areas except cognitive functioning, a concerning finding given that all but one study relied on parent reports of HRQOL without collateral information from the child[25,26,27]. This under appreciation of the impact of concussion/mTBI is likely not limited to parents/guardians, as mTBI is, largely, an invisible injury. These false perceptions may reduce the amount of school and sport accommodations, as well as family and peer support, which may further diminish a child's social and emotional wellbeing. These perceptions, and their effects, represent an area in need of further study.

While we attempted to characterize the longitudinal progression of HRQOL after mTBI, no typical course could be elucidated from the results. The changes in HRQOL over time were often isolated to individual HRQOL domains and the results were variable between studies[25,26,27,28,31,32]. This may due to the small number of studies and differences between patient populations resulting from varying definitions of mTBI.

Limitations/Future Directions:
One limitation of this review is that various definitions for mTBI were used across the studies. These heterogeneous definitions make it challenging to synthesize data from multiple studies and apply the results to clinical situations. For instance, it is unknown if the results of this review can be interpolated to the concussion population, as other clinical entities were included as well. This field would greatly benefit from consistent definitions of mTBI and concussion and a clear distinction between the two entities.

Furthermore, future studies should appreciate that the proportion of mTBI patients who experience poor outcomes is relatively small and, thus, the use of mean values could conceal the presence of this important subset of patients. This may explain the lack of significant differences between the mTBI groups and controls. Regardless, a subgroup of patients with poor outcomes appears to exist and deserves further study in order to better identify them and provide meaningful intervention.

There was also considerable heterogeneity in the timing of HRQOL measurements and thus we could not identify optimal timing of when HRQOL should be measured or when it should be expected to return to pre-injury scores. The lack of significant differences in HRQOL scores between time points may be explained by the fact that the first HRQOL measurement was one month or more post-injury in all studies that reported this information. By one month, the majority of mTBI patients may have recovered[3,9]. Future research efforts should attempt to measure

HRQOL more acutely, and more frequently throughout the course of mTBI recovery so the typical progression of HRQOL can be characterized, and patients with lower than expected HRQOL can be managed appropriately.

Prospective Case Series

A high proportion of study patients developed PCS, much higher than what has been described elsewhere. This is likely due to the fact that patients with a more substantial burden of illness are more likely to be referred to the specialist-run concussion clinic. The mean initial PedsQL score was low in all domains except social, and then improved steadily as patients recovered. The high initial social score explains why no significant week-to-week improvement was seen in this domain. It appears as though the quality of life aspects assessed by the social subscale are not significantly diminished in most adolescents with concussions. However, major deficits were noted in the other three domains analyzed. Most patients recovered by visit four, bringing the PedsQL score to a peak around this time point. The mean score then declines from that point on. This is a function of patients recovering and leaving the study, rather than the HRQOL of individual patients getting worse. Thus it appears as though these results are consistent with those identified in the systematic review, with a small proportion of patients experiencing lasting deficits in their HRQOL.

The domains most affected initially were the physical and cognitive functioning domains, as might be expected. However, as the study progressed, the psychosocial subscales became more prominently diminished than the physical domain. Although the mean social domain score was initially very high, this aspect of HRQOL began to deteriorate for patients who developed PCS and had 5 or more visits. This is likely because these patients were not participating in their regular activities and may have begun to experience social isolation as a result. These patients may be at greater risk fro developing adverse psychiatric outcomes. Psychosocial HRQOL is, therefore, an important target for monitoring and intervention in patients with prolonged recoveries.

Patients who went on to develop PCS had lower initial follow up visit HRQOL on all domains except social than those who did not develop PCS. This suggested that initial visit HRQOL may be a useful prediction tool to identify patients who will go on to develop PCS. Since the initial visit physical subscale score was the most different between the two groups ($p=0.0001$), ROC curve analysis was performed to identify an optimal cutoff score. A high sensitivity (0.895) and moderate specificity (0.667) for predicting those who will develop PCS were found to be achievable with a cutoff score of 82.81 on the initial physical subscale. Although identifying prediction tools for PCS was not initially a goal of this study, both this sensitivity and specificity are superior to those reported for the initial visit post-concussion symptom scale (sensitivity = 0.868, specificity = 0.624), a tool specifically designed to assess the symptoms of post-concussion syndrome[41]. Additionally, the physical subscale of the PedsQL is substantially shorter than the PCSS (8 items versus 22). Although the PCSS is a standard form for concussion patients in many clinics, the PedsQL is rarely administered in this setting. These results suggest that this approach may need to be revisited, as the PedsQL appears to provide additional benefit.

In addition to worse initial HRQOL, the HRQOL of patients who went on to develop PCS also improved more slowly. Therefore, minimal week-to-week improvement in HRQOL may be another useful warning sign for adolescents who may go on to have poor outcomes. Again, these patients should be monitored closely, and interventions should be provided as appropriate.

Limitations/Future Directions:
The major limitation of our characterization of the typical progression of HRQOL in adolescent concussion is the lack of a control group. This makes it difficult to differentiate the features of concussion from those of injury generally. In order to address this issue, we are currently conducting a follow-up study using adolescents with minor non-brain injuries (fractures, dislocations, 3rd degree sprains) as controls. To date, we have recruited approximately 125 adolescents with concussions, and approximately 85 adolescents with non-brain injuries for this study.

A second limitation to this study is its small size. Although it was adequately powered to show changes in HRQOL with time and to show differences between those who developed PCS and those who did not, a larger study is needed to confirm that the sensitivity and specificity of the initial visit PedsQL physical subscale for predicting those who will develop PCS is, in fact, superior to the PCSS. Again, this will be tested in our follow-up study.

Finally, the uncertainty around how to complete the school subscale when patients are not in school made these results impossible to interpret. A validated alternative calculation or scale is needed in order for the PedsQL to be of maximal utility year-round.

CONCLUSION

Pediatric mTBI is a clinical entity with few reliable objective measures to provide insight into a patient's progress, prognosis, and recovery. HRQOL is a validated and relevant, though often undervalued, outcome that can quantify recovery for both clinical and research purposes. A subset of mTBI/concussion patients who report substantially diminished HRQOL in some domains long after their injury was a consistent finding in both the published literature and our own prospective study. Careful attention is needed to identify these patients and intervene where possible. We identified the initial visit PedsQL physical subscale score as a potential prediction tool for PCS that may be superior to other prediction tools described in the literature. Further study will be needed to confirm this. Now that a basic understanding of the typical progression of HRQOL after pediatric mTBI/concussion has been established, the next step will be to study various interventions for their ability to improve HRQOL in these patients. HRQOL is a desirable outcome measure for this type of study because of its holistic nature and apparent sensitivity.

REFERENCES

1. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004 Feb;(43 Suppl):28-60.
2. US Department of Health and Human Services, Centers for Disease Control and Prevention. Heads up: facts for physicians about mild traumatic brain injury (MTBI). The Centers. 24 p.
3. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvorák J, Echemendia RJ, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Br J Sports Med. 2013 Apr;47(5):250-8
4. Giza CC, Hovda DA. The neurometabolic cascade of concussion. J Athl Train. 2001 Sep;36(3):228-35.
5. Duhaime AC, Beckwith JG, Maerlender AC, McAllister TW, Crisco JJ, Duma SM, et al. Spectrum of acute clinical characteristics of diagnosed concussions in college athletes wearing instrumented helmets. J Neurosurg. 2012 Dec;117(6):1092-9.

6. Blume H, Hawash K. Subacute concussion-related symptoms and postconcussion syndrome in pediatrics. Curr Opin Pediatr. 2012 Dec;24(6):724-30.
7. Cancelliere C, Hincapié CA, Keightley M, Godbolt AK, Côté P, Kristman VL, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil. 2014 Mar;95(3 Suppl):S210-29.
8. Hung R, Carroll LJ, Cancelliere C, Côté P, Rumney P, Keightley M, et al. Systematic review of the clinical course, natural history, and prognosis for pediatric mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil. 2014 Mar;95(3 Suppl):S174-91.
9. Collins M, Lovell MR, Iverson GL, Ide T, Maroon J. Examining Concussion Rates and Return to Play in High School Football Players Wearing Newer Helmet Technology: A Three-Year Prospective Cohort Study. Neurosurgery. 2006 Feb;58(2):275-86; discussion 275-86.
10. Boake C, McCauley SR, Levin HS, Contant CF, Song JX, Brown SA, et al. Limited agreement between criteria-based diagnoses of postconcussional syndrome. J Neuropsychiatry Clin Neurosci. 2004 Fall;16(4):493-9.
11. Ellis MJ, Leddy JJ, Willer B. Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: an evidence-based classification system with directions for treatment. Brain Inj. 2015;29(2):238-48.
12. Sady MD, Vaughan CG, Gioia GA. School and the concussed youth: recommendations for concussion education and management. Phys Med Rehabil Clin N Am. 2011 Nov;22(4):701-19.
13. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015 Jun 2:1-8.
14. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research; Center for Devices and Radiological Health. Guidance for Industry: patient-reported outcome measures: use in medical product development to support labeling claims. Rockville (MD): The Administration; 2009 Dec. 39 p.
15. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007 Jan 3;5:2.
16. Varni JW, Seid M, Rode CA. The PedsQL^{TM}: measurement model for the Pediatric Quality of Life Inventory. Med Care. 1999 February;37(2):126-39.
17. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. Qual Life Res. 1998 Jul;7(5):399-407.
18. Landgraf JM, Maunsell E, Speechley KN, Bullinger M, Campbell S, Abetz L et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Qual Life Res. 1998 Jul;7(5):433-45.
19. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res. 2001;10(4):347-57.
20. 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 Jun 10;29(9):1717-27.
21. Voss JD, Connolly J, Schwab KA, Scher AI. Update on the Epidemiology of Concussion/Mild Traumatic Brain Injury. Curr Pain Headache Rep. 2015 Jul;19(7):506.
22. Kiraly M, Kiraly SJ. Traumatic Brain Injury and Delayed Sequelae: A Review – Traumatic Brain Injury and Mild Traumatic Brain Injury (Concussion) are Precursors to Later- Onset

Brain Disorders, Including Early- Onset Dementia. ScientificWorldJournal. 2007 Nov 12;7:1768-76.
23. Scottish Intercollegiate Guidelines Network. SIGN [Internet]. Edinburgh: Healthcare Improvement Scotland; 2001-2009 [Updated 2015 Jun 29; cited 2015 Jul 13]. Available from: http://www.sign.ac.uk/.
24. World Health Organization . International statistical classification of disease and relation health problems. 10th ed. Geneva, Switz: World Health Organization; 1992.
25. Pieper P. Early outcomes from mild traumatic brain injury from child and proxy perspectives. [dissertation]. Orlando (FL): Barry University; 2009.
26. Pieper P, Bear M. Child and Proxy Perspectives of the Child's Health-Related Quality of Life 1 Month After a Mild Traumatic Brain Injury. J Trauma Nursing. 2011;18(1):11-17.
27. Pieper P, Garvan C. Health-related quality-of-life in the first year following a childhood concussion. Brain Inj. 2014;28(1):105-13.
28. Moran LM, Taylor HG, Rusin J, Bangert B, Dietrich A, Nuss KE, et al. Quality of Life in Pediatric Mild Traumatic Brain Injury and its Relationship to Postconcussive Symptoms. J Pediatr Psychol. 2012 Aug;37(7):736-44.
29. Yeates KO, Kaizar E, Rusin J, Bangert B, Dietrich A, Nuss K, et al. Reliable change in postconcussive symptoms and its functional consequences among children with mild traumatic brain injury. Arch Pediatr Adolesc Med. 2012 Jul 1;166(7):615-22.
30. Zonfrillo MR, Durbin DR, Koepsell TD, Wang J, Temkin NR, Dorsch AM, et al. Prevalence and risk factors for poor functioning after isolated mild traumatic brain injury in children. J Neurotrauma. 2014 Apr 15;31(8):722-7.
31. Petersen C, Scherwath A, Fink J, Koch U. Health-related quality of life and psychosocial consequences after mild traumatic brain injury in children and adolescents. Brain Inj. 2008 Mar;22(3):215-21.
32. Anderson V, Le Brocque R, Iselin G, Eren S, Dob R, Davern TJ et al. Adaptive ability, behavior and quality of life pre and posttraumatic brain injury in childhood. Disabil Rehabil. 2012;34(19):1639-47.
33. Waters E, Salmon L, Wake M. The parent-form Child Health Questionnaire in Australia: comparison of reliability, validity, structure, and norms. J Pediatr Psychol. 2000 Sep;25(6):381-91.
34. Huang IC, Thompson LA, Chi YY, Knapp CA, Revicki DA, Seid M, et al. The linkage between pediatric quality of life and health conditions: establishing clinically meaningful cutoff scores for the PedsQL. Value Health. 2009 Jul-Aug;12(5):773-81.
35. 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 Nov-Dec;3(6):329-41.
36. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry. 2001 Nov;40(11):1337-45.
37. Stein RE, Jessop DJ. Functional status II(R). A measure of child health status. Med Care. 1990 Nov;28(11):1041-55. Erratum in: Med Care. 1991 May;29(5):following 489.
38. American Association for Automotive Medicine. The Abbreviated Injury Scale (AIS): 1990 revision. Des Plaines (IL): The Association; 1990.
39. Babcock L, Byczkowski T, Wade SL, Ho M, Mookerjee S, Bazarian JJ. Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department. JAMA Pediatr. 2013 Feb;167(2):156-61.
40. Ellis M, Ritchie L, Koltek M, Hosain S, Cordingley D, Chu S et al. Psychiatric outcomes following pediatric sports-related concussion. J Neurosurg Pediatr. Forthcoming 2015.
41. Meehan WP 3rd, Mannix R, Monuteaux MC, Stein CJ, Bachur RG. Early symptom burden predicts recovery after sport-related concussion. Neurology. 2014 Dec 9;83(24):2204-10.

APPENDIX

Table 1: Overview of studies meeting systematic review inclusion criteria

Author, Year, Country	Study Design/ Control Group	mTBI/Concussion Case Definition	Sample Size	Age Range	HRQOL Scale
Petersen et al., 2008, Germany[31]	Observational study with two post-injury assessments (at first contact and 3 months later), compare to reference sample that is not described	mTBI: ICD-10 codes S02 (except SO2.5), S04, S06, S07 or S09	50	8-15	Parent-completed KINDL questionnaire[17]
Pieper, 2009/ Pieper & Bear, 2011/ Pieper & Garvan, 2014, U.S.[25,26,27]	Observational case-control comparing HRQOL of patients with mTBI, mild non-brain injuries and uninjured controls at baseline (pre-injury estimate) as well as 1, 3, 6 and 12 months post-injury	mTBI: non-penetrating head trauma resulting in a GCS of 13-15 upon presentation or 30 minutes post injury (whichever occurred later) with at least 1 of the following: a) a maximum 30 minute loss of consciousness, b) amnesia lasting a maximum of 24 hours, c) disorientation or confusion d) seizures, neurological signs or a non-operative intracranial lesion	38	5-17	Proxy and child completed PedsQL core and cognitive functioning scales[16]
Anderson et al., 2012, Australia[32]	Observational study with baseline (preinjury estimate) and 6-month post injury assessments for children with mild, moderate and severe TBI	mTBI: admitted to hospital for TBI, documented altered level of consciousness, lowest GCS between 13-15 with no neurological or radiological abnormalities	130	6-14	Parent completed Australian adaptation of the Child Health Questionnaire (CHQ)[33]
Moran et al. 2012/ Yeates et al., 2012, U.S.[28]	Observational case-control study comparing HRQOL in children with mild TBI to those with orthopedic injuries using HRQOL assessments at baseline (pre-injury estimate), 3 months post-injury and 12 months post-injury, and looking for correlations with reliable increases in post-concussion symptoms	mTBI: one of the following: observed loss of consciousness, GCS of 13 or 14, or at least two of the following: amnesia, vomiting, nausea, headache, diplopia, dizziness, disorientation, or any other indications of mental status change	186	8-15	Parent completed 50-item Child Health Questionnaire (CHQ-PF50)[18]

Zonfrillo et al., 2014, U.S.[30]	Observational study looking for predictors of poor HRQOL with assessments at baseline (pre-injury estimate) and at 3 and 12 months post-injury	mTBI: Any period of transient confusion, disorientation, impaired consciousness or amnesia lasting <24h, or signs of other neurological or neuropsychological dysfunction, with the worst GCS of 13-15 at initial evaluation and a GCS score of 15 at discharge or from the emergency department or at 24 h post-injury if hospitalized. Mild TBI was further subclassified into: mild I (no abnormalities on CT scans or no CT scans performed), mild II (skull fracture without intracranial hemorrhage) and mild III (intracranial hemorrhage). Only patients classified as mild I or II were included in the study.	329	2-17	Parent or adolescent completed PedsQL (adolescent completed if age 14 or older)[16]