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Establishing clinical cutoffs for the PedsQL™ Epilepsy Module

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ABSTRACT

Objective: The purpose of the present study was to establish clinical cutoffs for the PedsQL Epilepsy Module scales by dichotomizing scores into normative or impaired. We predicted that these cutoffs would be useful in identifying children at greater risk for impairments in health-related quality of life (HRQOL) including those who exhibit effects of ongoing seizures, antiepileptic drugs (AEDs), and polytherapy.

Methods: Two hundred and thirty-seven youth (2–18 years old) and their caregivers were recruited from five tertiary care hospitals across the United States. Caregivers and youth (5 years and older) completed the parent- or self-report versions of the PedsQL Epilepsy Module. Caregivers also completed measures of behavior and mood, AED side effects, and executive functioning in children. Clinical cutoffs were calculated in two ways: anchor-based (receiver operating characteristic (ROC) curve) and distribution-based (0.5 standard deviation (SD)). Medical characteristics were abstracted from the medical chart. t-Tests and chi-square tests were used to determine whether children's HRQOL classified as normative or impaired in epilepsy quality of life differed on seizure freedom, AED side effects, and polytherapy.

Results: The final clinical cutoffs were as follows for each PedsQL Epilepsy Module subscale (caregiver and child): Impact (Parent = 60.7; Child = 64.39), Cognitive (Parent = 38.11; Child = 50.97), Executive Functioning (Parent = 46.65; Child = 57.15), Sleep (Parent = 42.07; Child = 43.90), and Mood/Behavior (Parent = 54.14; Child = 53.30). Youth with more severe AED side effects, ongoing seizures, and/or on polytherapy were more likely to have impaired quality of life across domains.

Conclusion: Clinical cutoffs extend this instrument's utility in surveilling common psychosocial comorbidities, tracking changes in functioning over time, and informing clinical decision-making in youth with epilepsy including recommendations for additional assessment and intervention by a range of health providers serving youth with epilepsy (YWE).

1. Introduction

Pediatric epilepsy is associated with a wide range of physical, cognitive, and psychosocial comorbidities [1–4] related to seizures, antiepileptic drug (AED) side effects, and neuropathology that can have major impacts on child and family well-being. Patient-reported outcomes (PROs) are an important tool to evaluate the perceived impact of disease and treatments on individual functioning. One type of PRO that has been extensively used in the literature is health-related quality of life (HRQOL), a multidimensional outcome that measures physical, social, academic, and emotional functioning [5,6]. The PedsQL™ Epilepsy Module is a newly validated instrument that assesses HRQOL in youth with epilepsy ages 2–25 years [7,8]. Parallel self-report and parent-proxy versions capture perceptions of functioning over time, which can then lead to information sharing between patients and providers with the goals of reducing seizure burden, minimizing AED side effects, screening for cognitive and psychosocial comorbidities, and optimizing HRQOL.

Similar to several HRQOL measures, the PedsQL™ Epilepsy Module currently lacks established clinical cutoffs, which limit its ability to identify clinically meaningful concerns in clinical practice. Clinical cutoffs enable clinicians to quickly categorize patients into "high" versus "low" risk classifications to inform treatment recommendations, including changes to the treatment regimen and/or need for additional diagnostic testing related to psychological functioning. Unfortunately, there is no gold standard for establishing clinical cutoffs in the literature [9–12]. Two methods have been used to date: anchor-based and distribution-based approaches. An anchor-based approach [13] includes balancing sensitivity (highest proportion of true positives) and

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specificity (highest proportion of true negatives). Receiver operating characteristic (ROC) curve is one method to identify clinical cutoffs with equal sensitivity and specificity. However, ROC curves require a dichotomous "state" variable that defines the participant's actual impairment or dysfunction, such as a cutoff score from another well-established measure. In contrast, distribution approaches compare the change in PRO scores to some measure of variability such as the standard error of measurement (SEM), the minimally clinically important difference (MCID), or the standard deviation (SD) [14,15]. This approach is considered more statistically rigorous than using anchor-based approaches to define cutoff groups; however, distribution-based values can vary based on the variability in the sample.

To improve the clinical utility of the PedsQL™ Epilepsy Module, the aims of the current study were as follows: 1) to generate clinical cutoffs for each subscale of the PedsQL™ Epilepsy Module using both anchor-based and distribution-based methods to calibrate optimal screening clinical cutoffs and 2) to determine whether the cutoffs align with clinically meaningful groups (e.g., AED side effects, AED monotherapy versus polytherapy, seizure freedom) based on established and robust epilepsy-specific predictors of HRQOL. Youth with more AED side effects, polytherapy, and ongoing seizures were hypothesized to be more likely to have impaired HRQOL.

2. Methods

2.1. Participants

Children 5–18 years of age and caregivers of children ages 2–18 years of age diagnosed with epilepsy were recruited from five pediatric tertiary care centers across the United States for a larger national validation study of the PedsQL™ Epilepsy Module (see Modi et al., 2017 for methodological details [8]). Inclusion/exclusion criteria included 1) the ability to read English because of questionnaires only being validated in English, 2) no other chronic medical condition (e.g., diabetes), with the exception of allergies and neurobehavioral comorbidities (i.e., intellectual disability, attention-deficit/hyperactivity disorder and autism spectrum disorder).

2.2. Procedure

Participants were recruited by research personnel during epilepsy care clinic visits. Caregiver consent and child assent were obtained. Data were collected between August 2014 and March 2016. Participants completed questionnaires based on their age. Children with severe neurodevelopmental disorders did not complete self-report questionnaires. Medical chart reviews were conducted by research staff. Families received modest gifts cards for compensation for their time. The study was approved by each site's Institutional Review Board.

2.3. Measures

The PedsQL™ Epilepsy Module [7,8] has parallel parent and child versions for ages 5–18 years (Young Child, Child, and Teen subgroups), and parent-report only for toddlers ages 2–4 years. The measure has five domains: Impact, Mood/Behavioral, Sleep/Fatigue, Executive Functioning, and Cognitive. There is no overall HRQOL of score for this instrument. Domains and items are generally consistent across all versions but adjusted for language (i.e., simplified for younger children) and content (e.g., teen version includes driving). Each domain assesses the extent to which epilepsy and/or its treatments affect child HRQOL by asking how much of a problem the item has been in the past month on a 5-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = always a problem). Responses are reverse scored and linearly transformed to a 0–100 scale, with higher scores reflecting better HRQOL [7,8].

The Behavior Rating Inventory of Executive Function (BRIEF [16]) is an established and reliable 86-item parent- and 80-item self-report assessment of executive functioning. The overall Global Executive Composite T-score was used to classify individuals as follows: normative (T-scores <60), at-risk (T-score 60–65), or clinically elevated (T-scores ≥65). To ensure sensitivity to both at-risk and clinically elevated symptoms, individuals who fell into these groups were collapsed into one "at-risk/clinical" group.

The Behavior Assessment Schedule for Children-2nd Edition (BASC-2 [17]) provides parent-reported (BASC-2:PRS; 2–18 years) and self-reported (BASC-2:SRP; 8–18 years) assessments of emotional and behavioral difficulties. The BASC-2:PRS composite scores include Internalizing Behaviors (IBT; e.g., anxiety, depression), Externalizing Behaviors (EBT; e.g., hyperactivity, aggression), Behavioral Symptom Index (BSI; e.g., inattention, withdrawal), and Adaptive Skills (e.g., social skills, communication). The BASC-2:SRP composite scores include School Problems (e.g., attitudes to school, attitudes to teachers), Internalizing Problems (e.g., locus of control, sense of inadequacy), Emotional Symptom Index, Inattention/Hyperactivity, and Personal Adjustment (e.g., relations with parents, self-esteem). Standardized T-scores are calculated, with scores less than 65 representing normative levels, 65–69 representing at-risk status, and scores ≥70 representing clinical elevations. Similar to the BRIEF, we dichotomized those with at-risk/clinical scores into one group.

The Pediatric Epilepsy Side Effects Questionnaire (PESQ [18]) is a 19-item measure of AED side effects in children ages 2–18 years with epilepsy. Items assess the severity of neurological, behavioral, cognitive, weight, and motor side AED effects. Items are summed to obtain a total AED side effects score. The measure has strong psychometrics [18].

The PedsQL™ Family Information Form/Background Questionnaire was completed by caregivers providing general information about the child's age, caregiver work history, school absences, hospitalizations, and comorbid diagnoses. A medical chart review standardized across sites gathered data regarding epilepsy type [19] and treatment, seizure burden, treatment, seizure frequency in the past three months, and medical and psychosocial comorbidities.

2.4. Statistical analysis

Receiver operating characteristic curves (i.e., anchor-based method) and SDs (i.e., distribution-based method) were used to determine clinical cutoffs. For screening, the goal is to optimize the balance between sensitivity (accurately categorizing true positive cases) and specificity (accurately categorizing true negative cases). In other words, a trade-off between sensitivity and specificity exists. Specifically, as the cutoff is decreased, the sensitivity decreases, while the specificity increases. Youden's Index can be used to balance sensitivity and specificity [20] and is calculated as the value at which these two concepts are maximized.

Our anchor-based benchmark measure for the Executive Functioning subscale of the PedsQL™ Epilepsy Module is the parent-reported BRIEF global executive composite score, with at-risk/clinical elevations defined as T-scores ≥60 and normative defined as T-scores <60.

Similarly, the benchmark measure for the Mood/Behavioral subscale of PedsQL™ Epilepsy Module are any at-risk or clinical elevations (T-scores on any of the subscales ≥65) on the Externalizing, Internalizing, and Behavioral Symptom Indices of the BASC-2:PRS. No benchmark measures were available in the larger study [8] for the PedsQL™ Epilepsy Module Impact, Sleep, and Cognitive subscales so those cutoffs were developed solely using the distribution-based approach. As previously described, distribution-based clinical cutoffs were determined by examining scale scores >1/2 SD below the mean (as lower scores indicate more impaired HRQOL) for all the PedsQL™ Epilepsy Module

Table 1
Demographic data (n = 237).

	(%) or M ± SD
Age	11.3 ± 3.9 years
Female sex	44%
Race/ethnicity	
White: Non-Hispanic	60%
White: Hispanic	13%
Black: Non-Hispanic	16%
Black: Hispanic	0.4%
Asian/Pacific Islander	5%
Bi/multiracial or other	6%
Seizures in the past three months	
Yes	56%
No	44%
Seizure type	
Focal	49%
Generalized	37%
Unknown	14%
Years since diagnosis	4.4 ± 3.8 years
Number of antiepileptic drugs	1.3 ± 0.62 AEDs
Monotherapy	76.5%
Polytherapy	23.5%
Participating caregiver	
Mothers	87%
Fathers	10.5%
Other	2.5%

subscale. When discrepancies between the anchor- and distribution-based methods were identified, the clinical cutoffs from each method were averaged to create a final cutoff value for the PedsQL™ Epilepsy Module subscales.

To assess the validity of the established final PedsQL™ Epilepsy Module clinical cutoff scores, patients were dichotomized into “normative” (at or above the subscale clinical cutoff) or “impaired” (scores below the subscale clinical cutoff). The groups were then compared on established epilepsy-specific predictors of HRQOL (i.e., seizure freedom, monotherapy versus polytherapy, AED side effects) using independent t-tests and χ^2 tests of independence to further test the validity of the newly established cutoff scores (i.e., are children with known risk factors more likely to fall into the impaired category).

3. Results

3.1. Sample sociodemographic and medical data

The sample included 237 youth with epilepsy and their caregivers. Table 1 outlines the sociodemographic and medical characteristics of the sample.

3.2. Clinical cutoffs for each subscale of the PedsQL™ Epilepsy Module

Distribution- and anchor-based clinical cutoffs are presented in Table 2. The final clinical cutoffs were as follows for each PedsQL™ Epilepsy Module subscale (parent and child): Impact (Parent = 60.7; Child = 64.39), Cognitive (Parent = 38.11; Child = 50.97), Executive Functioning (Parent = 46.65; Child = 57.15), Sleep (Parent = 42.07; Child = 43.90), and Mood/Behavior (Parent = 54.14; Child = 53.30).

3.3. Do the clinical cutoffs differentiate between clinically meaningful groups?

3.3.1. AED side effects

t-Tests revealed significant differences between youth who were impaired versus those who were not on the PedsQL™ Epilepsy Module subscales on AED side effects (see Fig. 1): Parent-reported Impact (t (224) = 7.3; p < 0.001); Parent-reported Cognitive (t (224) = 7.3, p < 0.001); Parent-reported Executive Functioning (t (233) = 7.8, p < 0.001); Parent-reported Sleep (t (224) = 5.7, p < 0.001); Parent-reported Mood/Behavior (t (224) = 4.3, p < 0.001); Child Impact (t (233) = 2.8, p < 0.01); Child Cognitive (t (224) = 2.0, p < 0.05); Child Executive Functioning (t (224) = 2.5, p < 0.05); and Child Mood/Behavior (t (224) = 3.6, p < 0.001). Specifically, higher AED side effects were associated with lower HRQOL. No significant group differences were found for Child Sleep (t (224) = 1.9, p = ns).

3.3.2. Number of AEDs

χ^2 analyses revealed significant differences in the proportion of patients on AED monotherapy versus polytherapy for those who had poor versus those who had good HRQOL on PedsQL™ Epilepsy Module parent-reported subscales: Impact (χ^2 (1) = 38.9; p < 0.001); Cognitive

Table 2
Clinical cutoff methods for the PedsQL™ Epilepsy Module.

PedsQL Epilepsy Module subscales	T-score and clinical impairment-based method		0.5 SD method (PEDSQL)		Youden's		Final clinical cutoff (average or 0.5 SD method)	
	No benchmark measure							
	Parent	Child	Parent	Child	Parent	Child	**Parent**	**Child**
Impact (average score)	N/A		60.7	64.39	N/A		**60.7**	**64.39**
% of patients impaired	N/A		28.2%	29.9%	N/A			
	No benchmark measure							
	Parent	Child	Parent	Child	Parent	Child	**Parent**	**Child**
Cognitive	N/A		38.11	50.97	N/A		**38.11**	**50.97**
% of patients impaired	N/A		35.9%	36.4%	N/A			
	Parent-BRIEF global executive composite elevations							
	Parent	Child	Parent	Child	Parent	Child	**Parent**	**Child**
Executive Functioning	45.83	54.17	42.05	48.95	52.08	68.33	**46.65**	**57.15**
% of patients impaired	42.6%		36.3%	32.1%				
	No benchmark measure							
	Parent	Child	Parent	Child	Parent	Child	**Parent**	**Child**
Sleep	N/A		42.07	43.9	N/A		**42.07**	**43.9**
% of patients impaired	N/A		42.7%	33.0%	N/A			
	Parent-BASC (any EPT, IPT, BSI elevation)							
	Parent	Child	Parent	Child	Parent	Child	**Parent**	**Child**
Mood/Behavior	56.25	55.0	53.55	53.01	55.63	52.50	**54.14**	**53.50**
% of patients impaired	40.7%		32.5%	32.4%				

EPT: Externalizing Problems T score; IPT: Internalizing Problems T score; BSI: Behavioral Symptoms Index T score.
The bold text signifies the final clinical cutoff scores.

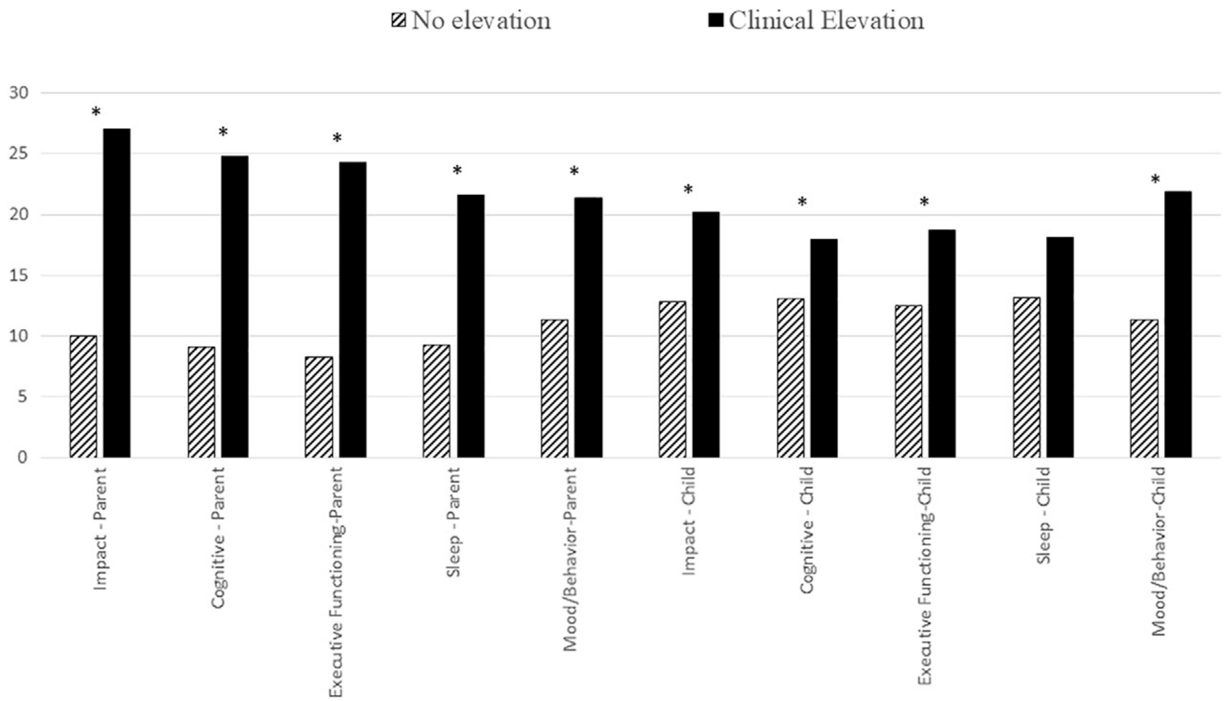

Fig. 1. Differences in total antiepileptic drug side effects based on clinical cutoffs of the PedsQL Epilepsy Module. *Significant group differences.

(χ^2 (1) = 26.2; $p < 0.001$); Executive Functioning (χ^2 (1) = 15.5; $p < 0.001$); Sleep (χ^2 (1) = 14.2; $p < 0.001$); and Mood/Behavior (χ^2 (1) = 4.9; $p < 0.05$) (see Fig. 2). These were all in the expected directions. For example, for the youth on monotherapy, a higher proportion demonstrated better HRQOL (i.e., above clinical cutoff) compared with those who were below the HRQOL clinical cutoff. No significant group differences were found for any of the child subscales: Impact (χ^2 (1) = 2.5; p = n.s.), Cognitive (χ^2 (1) = 0.27; p = n.s.), Executive Functioning (χ^2 (1) = 1.7; p = n.s.), Mood/Behavior (χ^2 (1) = 0.54; p = n.s.), and Sleep (χ^2 (1) = 0.04; p = n.s.).

3.3.3. Seizures

χ^2 analyses also revealed significant differences in the proportion of patients with seizures in the past 3 months versus those who were seizure-free by clinically impaired or not on the PedsQL™ Epilepsy Module for the following parent-reported subscales: Impact (χ^2 (1) = 28.8; $p < 0.001$); Cognitive (χ^2(1) = 11.1; $p < 0.001$); Executive Functioning (χ^2 (1) = 16.2; $p < 0.001$); and Sleep (χ^2 (1) = 5.9; $p < 0.05$). No significant group differences were found for the Mood/Behavior subscale (χ^2 (1) = 2.5; p = n.s.) nor any of the child subscales: Impact (χ^2 (1) = 3.7; p = n.s.), Cognitive (χ^2 (1) = 1.0; p = n.s.), Executive Functioning (χ^2

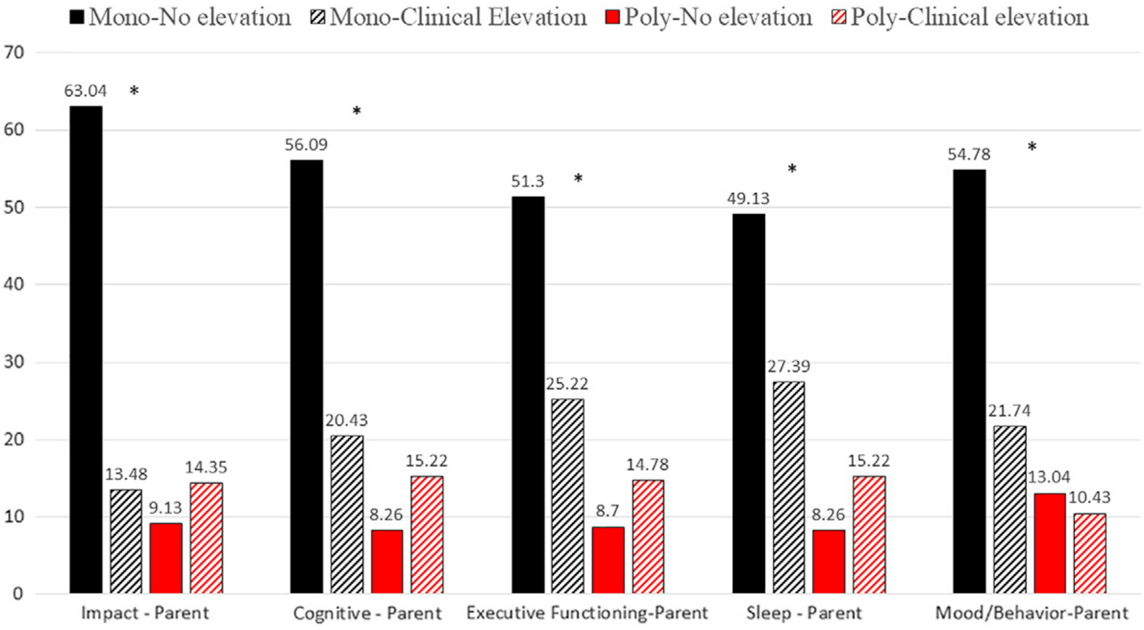

Fig. 2. Proportions of youth on monotherapy versus polytherapy based on clinical cutoffs of the Parent PedsQL Epilepsy Module, *Significant group differences.

(1) = 0.08; p = n.s.), Mood/Behavior (χ^2 (1) = 1.1; p = n.s.), and Sleep (χ^2 (1) = 0.22; p = n.s.) (see Fig. 3). For the significant findings, all were in the expected directions. For example, for the youth who were seizure-free, a higher proportion demonstrated better HRQOL (i.e., above the clinical cutoff) compared with those who were below the HRQOL clinical cutoff.

4. Discussion

We used a novel and systematic approach to establishing clinical cutoffs for the PedsQL™ Epilepsy Module using a nationally representative sample of youth with both new-onset and refractory epilepsy and their caregivers. Anchor-based and distribution-based methodologies were used in combination to derive clinical cutoffs based on well-established psychological instruments and SDs in the current sample. These clinical cutoffs can be used to expediently assess meaningful domains of epilepsy-specific HRQOL salient to youth with epilepsy and their caregivers, track changes in functioning, and inform clinical decision-making such as changes to AED regimens, referrals for further assessment or treatment, as well as informing support services.

The newly established clinical cutoffs now allow epilepsy providers to rapidly determine when HRQOL scores indicate concerns for impaired cognitive, executive, mood/behavioral, and sleep functioning relative to other children and youth with epilepsy. Scores falling in the impaired range may prompt further assessment or additional referrals (e.g., behavioral health treatment, neuropsychological testing, psychiatry consultation, cognitive rehabilitation). For parent-reported scores, the clinical cutoffs generated for the subscales aligned in the expected directions for AED side effects, polytherapy, and for seizures occurring within the past three months. Specifically, caregiver reports of youth experiencing more AED side effects, on polytherapy, or having continued seizures were more likely to report clinically impaired HRQOL across subscales. This builds on the extant research suggesting that these medical factors play a significant role in the HRQOL of youth with epilepsy [21–26]. One exception was the lack of significant findings on the parent-reported mood/behavior HRQOL subscale based on seizure presence/absence. Parents may observe disturbances in mood or behavior apart from seizure burden, and past research has shown that psychosocial comorbidities may be present and detrimental to HRQOL even with seizure freedom [27].

Children and youth reported links between higher AED side effects and greater impairments in Impact, Cognitive, Executive Functioning, and Mood/Behavior quality of life subscales, which is consistent with literature highlighting the detrimental impact of AED side effects on HRQOL [24]. In contrast, seizure freedom and number of AEDs (monotherapy vs polytherapy) were not identified by youth as factors significantly related to their HRQOL. One possible reason for the discrepancy in parent and child/youth results pertains to the unique perspectives they each have. For example, caregivers are more often tasked with tracking changes in functioning as it relates to changes in medical status or treatment regimen and may be more aware of how those factors influence HRQOL. Caregivers and children provide unique perspectives on HRQOL, and an aggregate approach is best to obtain a comprehensive perspective on functioning [28]. While obtaining both viewpoints can be helpful, given that caregivers are typically the gatekeepers for children's medical care and instrumental in guiding treatment decisions, caregiver report should be given priority in a clinical setting if time is constrained.

This study had notable strengths including a large sample size, a nationally representative sample of youth with epilepsy and their caregivers, and the use of well-established measures of psychological functioning. Unfortunately, this study did not have additional validated measures of sleep or cognitive functioning, and accordingly, it will be important for future studies to validate these clinical cutoffs against established instruments. Another limitation of this study is that we were not able to obtain self-report from older school age children or adolescents on the BASC-2:SRP.

Taken together, the clinical cutoffs established in the current paper for the PedsQL™ Epilepsy Module allow providers an enhanced and efficient clinical tool to evaluate the impact of epilepsy across domains of HRQOL, identify clinical impairment, and inform changes in treatment or the need for additional interventions. This study highlights that youth with greater seizure burden, polytherapy, or greater AED side effects are at particular risk for impaired HRQOL. Caregivers and their youth both offer valid and unique perspectives of HRQOL, and both should be considered when assessing HRQOL.

4.1. Clinical applications

The PedsQL Epilepsy Module is a readily accessible, brief measure that can be used during routine epilepsy visits to screen for psychosocial

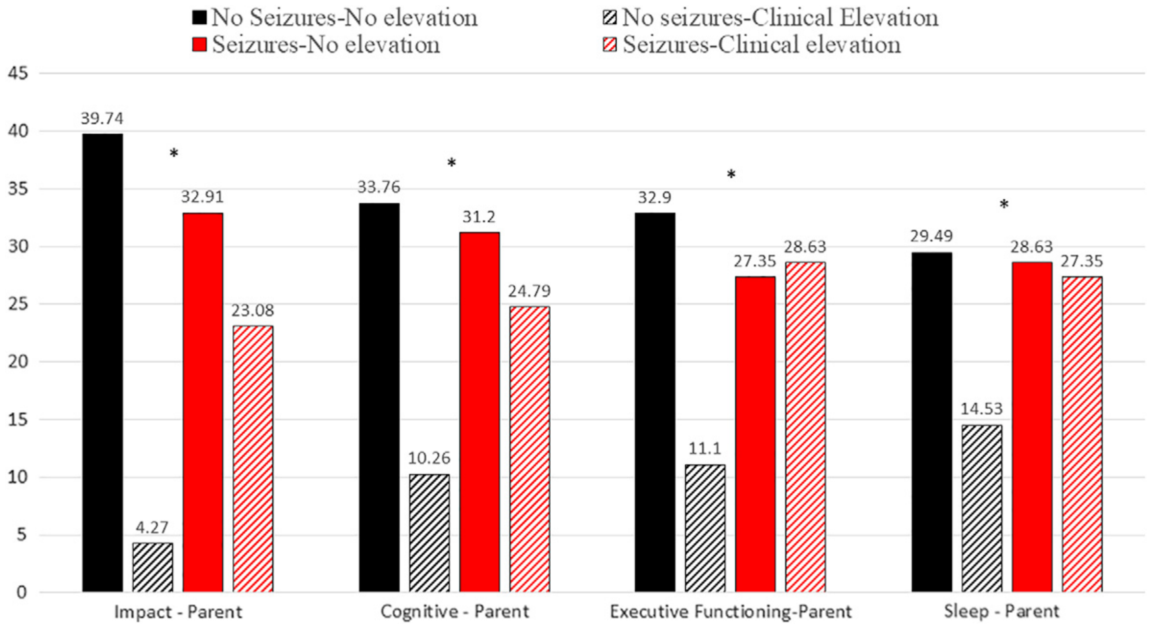

Fig. 3. Proportions of youth with and without seizures (past 3 months) based on clinical cutoffs of the Parent PedsQL Epilepsy Module. *Significant group differences.

functioning and tracking changes in status over time. Establishment of clinical cutoffs provides pertinent information for allied health providers to quickly assess whether patients are reporting significant difficulties in HRQOL domains and recommend appropriate referrals. The brevity of the measure allows for quick completion by youth and their caregivers in the waiting room prior to the clinic visit. The measure can be calculated and scores readily available for the visit by the allied health provider. Overall, the measure is a clinically useful tool to integrate behavioral healthcare into routine epilepsy care [29].

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Declaration of competing interest

None.

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