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FULL-LENGTH ORIGINAL RESEARCH

Trajectories of health-related quality of life in children with epilepsy: A cohort study

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Summary

Purpose: **Little is known about subgroups of children with epilepsy who may experience less favorable outcomes over time. The objectives of this study were to document trajectories of health-related quality of life (HRQL) and to identify predictors of the trajectory group in children with new-onset epilepsy.**

Methods: **Data were obtained from the Health Related Quality of Life in Children with Epilepsy Study, a prospective multisite study of children 4–12 years old with new-onset epilepsy followed for 24 months. Health-related quality of life was measured using the Quality of Life in Childhood Epilepsy questionnaire. Trajectories of HRQL were investigated using latent class trajectory modeling. Multinomial logistic regression was used to identify child, parent, and family predictors of HRQL trajectories.**

Key Findings: **A total of 374 families responded at baseline and 283 (76%) completed the study. Five HRQL trajectories were observed: *low-increasing* (4%), *moderate-decreasing* (12%), *moderate-increasing* (22%), *high-increasing* (32%), and *high-stable* (30%). Many children in the *low-increasing*, *moderate-increasing*, *high-increasing*, and *high-stable* had clinically meaningful improvements in HRQL: 82%, 47%, 63%, and 44%, respectively. In contrast, the majority of children in the *moderate-decreasing* group (56%) experienced clinically meaningful declines in their HRQL. Factors predicting trajectories were number of antiepileptic drugs prescribed, presence of comorbid behavior or cognitive problems, parent depression, and family functioning and demands.**

Significance: **Results suggested that children with epilepsy are not homogenous but rather consist of groups with different trajectories and unique predictors of HRQL. Problems associated with child behavior and cognition were the strongest predictors identified. Given that several risk factors are modifiable, it is important to examine these as potential targets within a family-centered framework to improve HRQL of children with new-onset epilepsy.**

KEY WORDS: **Cohort studies, Epilepsy, Family, Quality of life, Risk factors, Statistical models.**

Assessing health-related quality of life (HRQL) in children with epilepsy has important implications for their health care, as it may enhance understanding of the impact that epilepsy and its treatments have on children, allowing for more informed medical decisions. Indeed, health regulatory agencies now advocate for the evaluation of such patient-reported outcomes (PCORI, 2012).

Previous research has shown that children with epilepsy have compromised HRQL compared to healthy controls (Miller et al., 2003) and children with other conditions (Austin et al., 1994; Hoare et al., 2000). Few studies have prospectively assessed HRQL over time (Oostrom et al., 2003, 2005); previous longitudinal studies have provided

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basic comparisons in HRQL over time often based on presurgery and postsurgery assessments (van Empelen et al., 2005; von Lehe et al., 2006) of particular subsamples of patients with epilepsy (Jakovljevic et al., 2008), or describing single, *average* trajectories of change (Modi et al., 2011; Speechley et al., 2012).

In addition, previous research has documented that several clinical, psychosocial, and family environmental factors influence HRQL in children with epilepsy. Modi et al. (2011) observed seizure activity and medication side effects to be inversely associated with child HRQL. Sherman et al. (2007), Williams et al. (2003), and Yong et al. (2006) have all highlighted the strong correlation of behavior and cognitive problems with HRQL in children with epilepsy. Parental psychopathology, particularly maternal depression, poor family functioning, and high family stress appear to be consistent risk factors for worse HRQL (Fastenau et al., 2004; Austin et al., 2010; Ferro et al., 2011; Speechley et al., 2012).

Given the considerable variation in levels of HRQL we observed previously in children's HRQL during the first 24 months after diagnosis (Speechley et al., 2012), it is important to explore the extent to which distinct trajectories of change in HRQL exist that are not captured by modeling a single average trajectory of HRQL over time. Understanding patterns of differential risk for poor HRQL provides additional insight above and beyond previous investigations by identifying at-risk children and their families and the processes or factors by which these children become vulnerable. There is a dearth of rigorous evidence regarding health outcome trajectories in epilepsy in general, and in pediatric epilepsy in particular. This information may advance our understanding of which types of children have a propensity for poor or favorable HRQL over the course of epilepsy.

The objectives were the following: (1) to identify distinctive trajectories of HRQL over the first 24 months after diagnosis in children with epilepsy; and (2) to examine factors predicting individual trajectories of HRQL. Although the method used to identify trajectories of HRQL is relatively new and largely data-driven, we hypothesized three HRQL trajectories would be identified (increasing, decreasing, and stable) and that both clinical and psychosocial factors, particularly epilepsy-related comorbidities and family environment factors, would be associated with distinctive trajectories of HRQL. In other words, favorable trajectories of HRQL would be associated with less severe clinical and psychosocial factors (comorbidities and family environment), whereas less favorable trajectories would be associated with more severe clinical and worse psychosocial factors.

Methods

Sample

The sample for this study has been described elsewhere (Speechley et al., 2012). Briefly, data were collected in the Health-Related Quality of Life Study in Children with Epilepsy Study (HERQULES), a multicenter prospective cohort study of children 4–12 years of age newly diagnosed with epilepsy. Pediatric neurologists across Canada seeing children with new-onset epilepsy approached parents of eligible children about the study. Inclusion criteria were children 4–12 years of age presenting as a new case of epilepsy (≥2 unprovoked seizures), in whom diagnosis had not been confirmed previously, seen for the first time by a pediatric neurologist, and who had a parent with sufficient English language skills and that was primarily responsible for the child's care for at least 6 months. Children with major comorbid, nonneurologic conditions known to affect HRQL (e.g., asthma requiring daily medication) were excluded. Parents and neurologists completed four mailed questionnaires: postdiagnosis (baseline), and 6, 12, and 24 months later. Neurologists completed a brief form providing clinical information. Of the 456 eligible children, 374 (82%) parents returned completed postdiagnosis questionnaires. A total of 283 (62%) completed all four questionnaires. Baseline questionnaires were sent to participants 20 days postdiagnosis, on average, and 73% completed the baseline questionnaire within 6 weeks of diagnosis. The study protocol received approval from all relevant ethics boards.

Measures

Children's HRQL was assessed using the 76-item, parent-report, epilepsy-specific Quality of Life in Children with Epilepsy Questionnaire (QOLCE; Sabaz et al., 2003). The composite HRQL score is the unweighted average of 16 QOLCE subscales, ranging from 0 to 100. Higher scores indicate better HRQL. The QOLCE has been found to be valid and reliable (Sabaz et al., 2000, 2003). In HERQULES, Cronbach's $\alpha = 0.92$.

Severity of epilepsy was assessed with the neurologist-reported Global Assessment of Severity of Epilepsy (GASE; Speechley et al., 2008), a single-item measure where neurologists rated the overall severity of each child's epilepsy since their last visit using a 7-point scale, with lower scores indicating more severe epilepsy. The GASE demonstrated adequate validity and reliability (Speechley et al., 2008).

Neurologists also reported on seizure type (generalized; localization-related [partial]; partial onset, secondary generalization; undetermined) and frequency (7-point scale ranging from "not at all frequent" to "extremely frequent"), side effects (same 7-point scale), medication, and age of onset. Seizure frequency was based on an overall assessment by the neurologist regarding the period since the last clinic visit. Children rated as "not at all frequent" may have included children in remission. Neurologists rated the presence of behavior or cognitive problems using single-item measures by scoring each child as having severe, moderate, mild, or no problems. Given the distribution of scoring, child behavior and cognitive problems were then recoded as

either present or absent. Evaluation of child cognitive and behavior problems noted by the neurologist during each visit were not based on any formal diagnostic assessments, unless additional information was provided by the parent or teacher, or neuropsychological records obtained from the school or hospital at the time of diagnosis or thereafter.

Parents completed four measures describing family environment. The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR) was used to assess satisfaction with family relationships (Smilkstein, 1978). It is a five-item instrument using a 5-point Likert response scale with higher scores (range 0–20) indicating greater satisfaction. The Family APGAR has been found to be valid and reliable (Smilkstein, 1978; Smilkstein et al., 1982). The Family Inventory of Resources for Management (FIRM) was utilized to assess resources available to aid families' adaptation to stressful events (McCubbin et al., 1996b). For this study, two subscales (family mastery and health, extended family social support) found to be associated with adaptation to childhood epilepsy were used (Austin et al., 1992). Higher scores indicate more family resources (24 items, range: 0–72). The FIRM has demonstrated adequate reliability and validity (McCubbin et al., 1996b). Family demands were quantified using the 71-item Family Inventory of Life Events and Changes (FILE), which assesses changes in life events experienced by a family during the previous year (McCubbin et al., 1996a). Higher scores indicate more demands (range: 0–71). FILE's reliability and validity are well-established (McCubbin et al., 1996a).

Parent depression was measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item questionnaire designed to assess depressive symptoms over the past week (Radloff, 1977). The total score spans from 0 to 60, with higher scores indicating greater impairment.

Analysis

Children's HRQL was described using descriptive statistics and frequency distributions. Trajectories of HRQL were investigated using latent class growth curve modeling, which permits the modeling of multiple subgroup trajectories as opposed to a single average trajectory for the entire sample (Nagin, 2005; Ferro & Speechley, 2012). Model parameters were estimated using maximum-likelihood method approach, which used all individuals having ≥1 assessment, assuming data were missing at random. Baseline child, parental, and family characteristics previously found to be associated with HRQL were compared across trajectory groups using analysis of variance and chi-square tests. Multinomial logistic regression analysis was conducted to identify predictors of HRQL trajectories. A standard error of measurement (SEM) criterion was calculated for our sample at baseline (SEM = 4.01) and used to identify children who achieved clinically meaningful changes in HRQL (Wyrwich et al., 1999). Details of the analyses are described in Appendix S1.

Results

Sample characteristics have been described elsewhere (Speechley et al., 2012). At baseline (N = 374), children had a mean age of 7.5 (2.3) years and 52% were male. Thirty-nine percent of children had generalized epilepsy. The mean scores on the QOLCE and GASE were 70.5 (13.9) and 5.4 (1.2), respectively, indicating that children had relatively good HRQL and "somewhat severe" to "a little severe" epilepsy on average. Behavior and cognitive problems were found in 15% and 20% of children, respectively (7% had both). Children with complete data were less likely to have cognitive problems ($p = 0.0126$) compared to those lost during follow-up; however, no differences were observed for seizure type, epilepsy severity, behavior problems, or HRQL.

The mean age of parents was 37.6 (6.1) years at baseline. Parents were mostly married (81%), employed (67%), and had postsecondary education (67%). The mean score on the CES-D was 14.3 (10.3), and 33% of parents had clinically relevant levels of depressive symptoms (CES-D ≥ 16). Mean scores on family environment measures were the following: Family APGAR 13.9 (3.8), FIRM 50.1 (11.1), and FILE 9.5 (6.5). This indicated that families were functioning well, had adequate resources, and had relatively few demands on them. Compared to published norms, these families had significantly higher FIRM (48.0 [11.0]) and FILE scores (8.8 [5.9]) (McCubbin et al., 1996a,b) and significantly lower Family APGAR scores (16.4 [2.1]) (Smilkstein et al., 1982). Additional characteristics are shown in Table 1.

A five-group trajectory model was adopted for analysis, as it had the highest probability of being the correct model compared to models with the number of groups ranging from 3 to 7. The Bayesian Information Criterion (BIC) fit index was the lowest among competing models (−4481.9) and the mean posterior probability of group membership was 0.80, ranging from 0.70 to 0.86. All groups were best modeled with a linear slope, with the exception of group 4, which required the inclusion of a quadratic term to capture the concave shape of the trajectory. The predicted and observed trajectories of HRQL corresponded well, suggesting good model fit (Fig. 1).

Scores on the QOLCE for each group at each measurement occasion are shown in Table 2. The first trajectory consisted of children with low QOLCE scores at baseline that increased over time (*low-increasing*; n = 15, 4%). The second trajectory consisted of moderate baseline QOLCE scores that decreased (*moderate-decreasing*; n = 44, 12%). The third trajectory comprised moderate baseline QOLCE scores that increased from 63.2 to 69.5 (*moderate-increasing*; n = 84, 23%). In the fourth trajectory, children had high baseline QOLCE scores that increased substantially at 6 months, and then plateaued between 6 and 24 months (*high-increasing*; n = 120, 32%). In the fifth group of

Table 1. Characteristics of the study sample at baseline and 24 months[a]

	Baseline (n = 374)	24 months (n = 283)
Child characteristics		
Age (years)	7.5 (2.3)	9.5 (2.3)
Sex (%)		
Male	52.4	51.6
Female	47.6	48.4
Epilepsy syndrome type (%)		
Generalized	38.5	38.0
Localization-related (partial)	39.6	42.6
Partial onset, secondary generalization	20.0	16.7
Undetermined	1.9	2.7
Seizure frequency (%)		
Low	65.6	94.2
Moderate	11.4	4.0
High	23.0	1.8
No. AEDs currently prescribed (%)		
0	33.3	23.5
1	63.6	65.3
≥2	3.1	11.2
Quality of life, QOLCE	70.5 (13.9)	76.3 (13.9)
Epilepsy severity, GASE	5.4 (1.2)	6.3 (1.1)
Comorbidities (%)		
Behavior problems	15.1	23.4
Cognitive problems	19.5	29.1
Parent characteristics		
Age (years)	37.6 (6.1)	40.3 (5.6)
Sex (%)		
Male	7.2	7.1
Female	92.8	92.9
Marital status (%)		
Not married	19.3	17.4
Married[b]	80.7	82.6
Employment status (%)		
Not employed	32.9	23.0
Employed	67.1	77.0
Education (%)		
Primary school	1.9	0.4
Secondary school	31.5	23.8
Postsecondary school	66.6	74.8
Depressive symptoms, CES-D	14.3 (10.3)	11.8 (9.9)
Family characteristics		
Functioning, APGAR	13.9 (3.8)	14.1 (3.9)
Resources, FIRM	50.1 (11.1)	50.7 (11.5)
Demands, FILE	9.5 (6.5)	7.8 (5.7)
Annual household income (%)		
<$20,000	8.0	3.9
$20,000–39,999	14.3	11.5
$40,000–59,999	21.4	19.2
$60,000–79,999	20.4	20.4
≥$80,000	37.0	45.0

AEDs, antiepileptic drugs.
[a]Reported as mean (standard deviation), unless otherwise stated. Frequency distributions may not add up to 100% due to rounding or missing data.
[b]Includes those in married and common-law relationships.

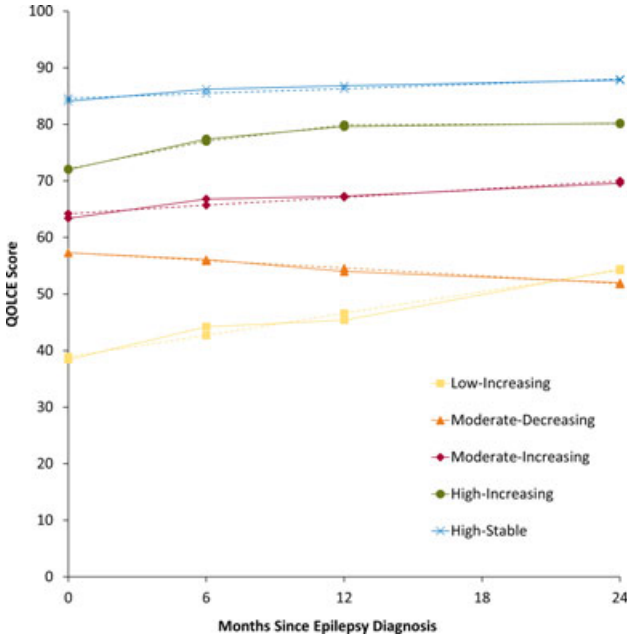

Figure 1.
Trajectories of children's health-related quality of life during the first 24 months after epilepsy diagnosis. Solid lines depict observed trajectories (mean QOLCE score) and dashed lines predicted trajectories.
Epilepsia © ILAE

children had persistently high QOLCE scores during the 24-month follow-up (*high-stable*; n = 111, 30%). QOLCE scores were significantly different across groups, except for the difference between the *low-increasing* and *moderate-decreasing* groups, which was not statistically significant at 24 months.

Across all groups combined, 50% of children had a clinical improvement and 18% had a clinical decline in HRQL (Speechley et al., 2012). Many children in the *low-increasing*, *moderate-increasing*, *high-increasing*, and *high-stable* had clinically meaningful improvements in HRQL: 82%, 47%, 63%, and 44%, respectively. In contrast, the majority of children in the *moderate-decreasing* group (56%) experienced clinically meaningful declines in their HRQL.

Table 3 summarizes the comparison of baseline child and family characteristics across trajectory groups. Significant overall differences among groups were observed for the number of antiepileptic drugs (AEDs) currently prescribed; child behavior and cognitive problems; parental depressive symptoms; and, family functioning, resources, and demands. No significant differences across trajectory groups were observed for seizure type or frequency at baseline (Table 3) or at 24 months ($\chi^2 = 7.62$, $p = 0.4710$; $\chi^2 = 7.33$, $p = 0.1197$).

Predictors of children's HRQL trajectories were examined using multinomial logistic regression, with only those variables demonstrating significant effects in the unadjusted analysis (odds ratios [ORs] and 95% confidence intervals [CIs] in Table 4). Using the *high-stable* group as the reference, the *low-increasing* group had more AEDs currently prescribed, more behavior and cognitive problems, parents

Table 2. Differences in children's health-related quality of life over 24 months by trajectory group[a]

Measurement	Low-increasing (n = 15)	Moderate-decreasing (n = 44)	Moderate-increasing (n = 84)	High-increasing (n = 120)	High-stable (n = 111)	F	p-Value
Baseline	38.6 (7.3)	57.6 (8.0)	63.2 (8.5)	71.6 (7.5)	84.8 (5.6)	229.7	<0.0001[b]
6 months	45.1 (8.1)	56.3 (8.8)	66.5 (7.2)	77.1 (5.8)	86.5 (5.3)	236.7	<0.0001[b]
12 months	45.6 (7.1)	54.1 (7.7)	66.8 (6.9)	79.8 (5.6)	87.0 (5.2)	281.6	<0.0001[b]
24 months	55.2 (13.6)	51.3 (8.4)	69.5 (5.3)	79.8 (7.6)	88.2 (5.1)	196.4	<0.0001[b]

[a]Reported as mean (standard deviation).
[b]No significant difference between *low-increasing* and *moderate-decreasing* groups.

Table 3. Comparison of baseline sample characteristics across trajectory groups[a]

	Low-increasing (n = 15)	Moderate-decreasing (n = 44)	Moderate-increasing (n = 84)	High-increasing (n = 120)	High-stable (n = 111)	F/χ^2	p-Value	Pairwise contrasts
Child characteristics								
Age (years)	7.2 (2.6)	7.5 (2.5)	7.5 (2.3)	7.5 (2.2)	7.3 (2.4)	0.22	0.9263	
Male (%)	47.1	63.4	53.2	48.8	50.0	2.54	0.6381	
Partial seizures (%)	56.3	56.1	59.5	60.3	63.9	3.63	0.8895	
Age at seizure onset	6.5 (3.3)	7.0 (2.4)	7.0 (2.3)	6.9 (2.5)	6.7 (2.4)	0.29	0.8860	
No. AEDs prescribed	0.9	0.9	0.7	0.7	0.6	3.45	0.0088	5 < 2
Epilepsy severity, GASE	5.5 (1.0)	5.0 (1.3)	5.3 (1.1)	5.5 (1.2)	5.5 (1.2)	2.19	0.0697	
Low seizure frequency (%)	47.1	65.9	65.0	66.2	71.3	4.09	0.3935	
Behavior problems (%)	56.3	26.8	21.5	12.9	2.8	41.40	<0.0001	5 < 1–4 4 < 1, 2 2, 3 < 1
Cognitive problems (%)	50.0	48.8	22.8	16.4	5.6	46.58	<0.0001	5 < 1–3 3, 4 < 1, 2
Parent characteristics								
Age (years)	36.9 (7.1)	37.8 (7.3)	37.7 (5.6)	36.9 (5.7)	38.6 (6.2)	1.14	0.3382	
Female (%)	100.0	97.6	94.9	92.3	88.9	5.77	0.2175	
Married (%)[b]	76.5	73.2	73.4	81.4	88.9	9.08	0.0593	
Employed (%)	70.6	70.7	60.3	66.4	71.0	2.77	0.5977	
College/University (%)	58.8	61.0	58.2	68.2	74.1	7.08	0.5299	
Depression, CES-D	22.4 (11.7)	17.7 (9.7)	16.3 (10.9)	14.9 (10.1)	9.6 (8.1)	11.42	<0.0001	5 < 1–4
Family characteristics								
Functioning, APGAR	10.9 (4.7)	12.3 (3.7)	13.0 (3.6)	14.2 (3.7)	15.4 (3.0)	11.59	<0.0001	5 > 1–3 4 > 1
Resources, FIRM	42.0 (11.4)	46.2 (11.4)	46.1 (10.4)	50.2 (10.5)	55.4 (9.9)	13.54	<0.0001	5 > 1–4
Demands, FILE	14.3 (6.5)	11.8 (6.6)	10.9 (7.0)	9.2 (6.6)	7.2 (4.9)	8.41	<0.0001	5 < 1–3 4 < 1
Income ≥$80,000 (%)	29.4	29.0	37.8	37.5	40.2	6.42	0.1706	

AEDs, antiepileptic drugs.
[a]Reported as mean (standard deviation), unless otherwise stated.
[b]Includes those in married and common-law relationships.

with more depressive symptoms, worse family functioning, and more family demands. The *moderate-decreasing* group was also prescribed AEDs, had more cognitive problems, worse family functioning, and more family demands. The *moderate-increasing* group had more behavior and cognitive problems, parents with more depressive symptoms, worse family functioning, and more family demands. The *high-increasing* group had parents with more depressive symptoms compared to the *high-stable* group.

Discussion

Five trajectories of HRQL were identified during the first 24 months after diagnosis. The largest group was composed of children with *high-increasing* QOLCE scores. The shape of this trajectory was similar to that of the HRQL trajectories described previously (van Empelen et al., 2005; Speechley et al., 2012). This trajectory described children with good HRQL at baseline with the greatest improvement

Table 4. Baseline predictors of children's health-related quality of life trajectory group[a]

	Low-increasing (n = 15)	Moderate-decreasing (n = 44)	Moderate-increasing (n = 84)	High-increasing (n = 120)	High-stable (n = 111)[b]
No. AEDs currently prescribed	**2.72 (1.30–5.70)**	**2.16 (1.14–4.10)**	1.07 (0.62–1.87)	1.48 (0.93–2.37)	1.00
Behavior problems	**18.65 (3.28–105.99)**	4.08 (0.92–18.04)	**5.57 (1.43–21.62)**	3.54 (0.95–13.25)	1.00
Cognitive problems	**5.67 (1.18–27.18)**	**10.18 (3.21–32.33)**	**3.29 (1.12–9.65)**	2.41 (0.88–6.61)	1.00
Parental depressive symptoms	**1.08 (1.01–1.15)**	1.05 (1.00–1.10)	**1.05 (1.01–1.09)**	**1.05 (1.01–1.09)**	1.00
Family functioning	**0.79 (0.66–0.94)**	**0.83 (0.73–0.94)**	**0.88 (0.80–0.97)**	0.96 (0.88–1.05)	1.00
Family demands	**1.13 (1.03–10.23)**	**1.10 (1.03–1.18)**	**1.09 (1.02–1.15)**	1.05 (0.99–1.11)	1.00

AEDs, antiepileptic drugs.
Predictors were identified using multinomial logistic regression. Significant associations are shown in bold.
[a]Reported as odds ratio (95% confidence interval).
[b]Reference group.

in HRQL during the first 6 months after diagnosis, which then plateaued. The mean QOLCE scores in the *high-increasing* trajectory were similar to those reported previously in a sample of children with benign rolandic epilepsy (Connolly et al., 2006). The second largest group consisted of children with *high-stable* HRQL who, for the most part, had the most favorable characteristics, including the lowest proportion of children with behavior or cognitive problems and more nurturing family environment. The third largest group was the *moderate-increasing* group, which was composed of children who had moderately good HRQL at baseline that increased over time. The next largest group had children with *moderate-decreasing* HRQL over time. This group had QOLCE scores similar to those of children with refractory epilepsy with intellectual disability (Sabaz et al., 2001). This finding is not surprising given that about half of the children in this trajectory group were reported to have cognitive problems and were comparable to children with intellectual disability. As this is the only group to demonstrate a decline in HRQL over time, they represent an important and substantial subset of children for further study to better understand the mechanisms contributing to unfavorable changes in HRQL. The smallest group consisted of children with *low-increasing* HRQL. This group of children had the largest improvement in HRQL between diagnosis and 24 months.

The discordance between our hypothesis of three trajectories and the observed results was attributable to the fact that we expected the *moderate-increasing, high-increasing,* and *high-stable* groups to form a single *stable* trajectory. However, collapsing these groups and re-specifying the model resulted in substantially worse model fit, suggesting that these trajectories represent distinct subgroups of children with epilepsy.

The predictive model demonstrated that fewer AEDs currently prescribed, fewer behavior and cognitive problems, fewer parental depressive symptoms, better family functioning, and fewer demands were associated with a more favorable HRQL trajectory. These associations have also been observed in previous cross-sectional studies: AEDs prescribed (Miller et al., 2003; Yong et al., 2006); behavior and cognitive problems (Williams et al., 2003; Yong et al., 2006; Sherman et al., 2007); parental depression (Adewuya, 2006; Wood et al., 2008); and family environment (Rodenburg et al., 2005). Risk factors identified were similar to baseline factors predicting average HRQL at 24 months in this sample (Speechley et al., 2012). Results from the current and previous studies allow these risk factors to be ranked in terms of strength in predicting HRQL in children with epilepsy: cognitive problems, behavior problems, number of AEDs prescribed, family functioning, family demands/stress, and parental depression. Although the exact ranking of these variables is arguable, they remain a robust set of risk factors in which to better understand changes in HRQL in children with epilepsy. Of importance, this study adds to the growing literature exposing the strong influence of family factors (Oostrom et al., 2003, 2005; Fastenau et al., 2004; Rodenburg et al., 2005; Austin et al., 2010; Speechley et al., 2012), which for some children, may have a greater impact on their HRQL compared to clinical characteristics of epilepsy.

Only three longitudinal studies, independent of the current work (Ferro et al., 2011), have prospectively documented factors for HRQL in children with epilepsy, and findings were mixed. Modi et al. (2011), reported that HRQL was stable over a 7-month period; seizures and adverse effects of medications predicted HRQL. Austin et al. (2010) observed that among children with a first seizure, mental health improved over time and family functioning protected against declines in children's self-esteem, a component of HRQL. In another study by Austin et al. (2011), behavior problems were observed to decrease during a 3-year follow-up in children with a first recognized seizure; family factors, including functioning and resources, were predictive behavior problems in these children. These studies reported average outcome trajectories and none conducted subgroup analysis.

Given that two domains of the QOLCE capture behavior and cognition, it was not surprising that child behavior and cognitive problems would exert a greater influence on HRQL compared to the other risk factors identified. However, the large effects observed were interesting: cognitive

problems were the strongest risk factor for the *moderate-decreasing* group and behavior problems were the strongest risk factor, followed by cognitive problems, for the *low-increasing* and *moderate-increasing* groups. The wide confidence intervals limit the utility of these estimates and can be attributed to the relatively small number of children with behavior or cognitive problems, especially in the *low-increasing* group. Therefore, the magnitude of these effects should be interpreted with caution. In addition, given that those participants lost to follow-up were more likely have to cognitive problems, the findings may underestimate the effect of cognitive problems on child HRQL over time. Despite having a large proportion of children with behavior and cognitive problems, the *low-increasing* and *moderate-increasing* groups showed improvement in their HRQL over time. This positive outcome should not distract from the importance of considering behavior and cognitive problems in an effort to achieve more favorable HRQL outcomes more rapidly for children and families.

This predictive model may be useful for physicians who are caring for children with epilepsy, in that it can identify children who are at particularly high risk for compromised HRQL. By assessing the extent to which children and their families match the collection of risk factors, the model can aid in predicting which HRQL trajectory a child newly diagnosed with epilepsy might follow. At a practical level, neurologists can use several tools to stratify children by risk into HRQL trajectories. One option, the two-item Patient Health Questionnaire, can screen parents for depression and is preferred for its brevity (Pignone et al., 2002). In the absence of other risk factors, children whose parents screen positive for depression are likely to be in the *high-increasing* trajectory. Although there is considerable overlap of risk factors for the remaining trajectories, patterns do emerge that allow neurologists to stratify patients. Review of the medical record and subjective assessment of behavior and cognitive problems can be used to predict HRQL trajectory—comorbid behavior and cognitive problems and multiple AED use suggest *low-increasing*; cognitive problems in isolation with multiple AEDs suggest *moderate-decreasing*; and comorbid behavior and cognitive problems suggest *moderate-increasing*. Furthermore, neurologists should observe family dynamic during clinical encounters and document cues indicative of family dysfunction and stress. Although clinical interpretation of latent class analysis is still its infancy, future research examining how changes in psychosocial and clinical risk factors over time influence HRQL trajectories could make an important contribution to pediatric epilepsy.

The risk factors identified may present avenues for intervention to improve unfavorable trajectories, specifically, those that encompass the family environment—parental depressive symptoms, family functioning, and family demands—as these risk factors are amenable to intervention through the adoption of family-centered care practices (Smith et al., 2002; Law et al., 2003). Family-centered care is a multidisciplinary model of health care delivery that can be adopted in pediatric neurology to include the following: psychology, psychiatry, social work, family counseling, and local epilepsy support centers immediately after diagnosis for proactive and prevention-based psychosocial care in an effort to optimize outcomes for families and children. Although clinical factors including epilepsy severity and seizure frequency were not associated with HRQL trajectories, number of AEDs was a risk factor. Given that AED use is strongly linked to epilepsy severity and seizure frequency (Perucca et al., 1998), it may be that AED use is a proxy for these clinical features, an indicator of the difficulty in managing a child's epilepsy. Furthermore, although an earlier study found that AED side effects were associated with worse HRQL (Modi et al., 2011), results from the current sample did not show differences in AED side effects across HRQL trajectories (data not shown). Instead, AED side effects were found to be associated with number of AEDs currently prescribed. Different methods of assessing AED side effects may also explain discrepant findings with previous research. Nonetheless, these clinical descriptors should be monitored and incorporated into the family-centered approach.

Given the heterogeneity of pediatric neurology clinics and the resources available to families, it is often difficult to operationalize family-centered care in the context of daily clinical care. Referrals to family counseling for each child diagnosed with epilepsy may not be feasible; instead referrals to community epilepsy support centers could be offered to families soon after diagnosis. In an effort to provide individualized care within the family-centered approach, clinicians should strive to be attuned to the family climate and proceed with recommendations (e.g., counseling for parental depression) on a case-by-case basis.

This study has several strengths. To our knowledge HERQULES is the first large-scale, multisite study to document HRQL in children with new-onset epilepsy. The relatively large sample and good initial participation and retention rates increase the external validity of findings. Second, this study utilized the QOLCE, an established instrument, to measure children's HRQL. Third, this study focused on incident rather than prevalent cases of childhood epilepsy. Results may be useful for clinicians as part of the initial consultation when diagnosing children with epilepsy to prevent unfavorable trajectories of HRQL during the first 24 months postdiagnosis. Identifying risk factors for specific subgroups of children has unique implications beyond prior findings such that targets for limited health care funding can be further narrowed and directed at children and families in greatest need in an effort to provide more individualized care.

This study also has limitations. First, the sample was recruited from pediatric neurology practices and may not

be representative of all families of a child with epilepsy, potentially limiting external validity. However, previous work demonstrated that it is feasible to recruit a representative population-based sample of children with epilepsy given that family physicians in Canada reported they would refer almost all of their patients with childhood epilepsy to a pediatric neurologist (Speechley et al., 1999). In addition, it is not possible to comment on trajectories of HRQL for children with major comorbid, nonneurologic conditions known to impact HRQL who were not studied in this sample. Compared to recent studies of HRQL in children with epilepsy (Taylor et al., 2011; Baca et al., 2012), our study reports on families where parents are more likely to be married and to have postsecondary education. However, it is important to note that our sample is in line with the Canadian population with regard to marital status and postsecondary education (HRSDC, 2013).

Second, as with all longitudinal studies, selection bias resulting from differential losses to follow-up may affect the validity of the results. Comparison of the trajectory-wise distribution of completers and those lost to follow-up were similar (Table S1) and assuage concerns regarding this potential bias. Although larger differences were apparent in the *high-increasing* and *high-stable* groups between completers and noncompleters, these trajectories showed minimal differences in the risk factor analysis further tempering this potential bias.

Third, there are two measurement limitations to note. The evaluation of cognitive and behavior problems are based on the subjective opinion of the pediatric neurologist and are not formal diagnoses based on any specified testing or diagnostic procedures. Therefore, the nature of such problems is difficult to evaluate in the context of the study findings. Furthermore, the clinical implications that can be drawn from the assessment of seizure frequency are somewhat limited by the lack of a numerical count of seizures within a specified time period.

Finally, because this study relied on parents' perceptions for both exposures and outcomes, there was potential for parents' reports to be biased, which would threaten the study validity. This phenomenon was investigated and results suggested no evidence of informant discrepancy (Ferro et al., 2010). In addition, no child self-report data were available. Due to the difficulty in obtaining reliable reports from very young children, parent informants were employed as valid proxy reporters (Theunissen et al., 1998). However, recent evidence in pediatric neurology suggests that there may be discordance between parent and child self-reports of child HRQL (Baca et al., 2010).

Conclusion

Our study suggests that children newly diagnosed with epilepsy are not homogeneous but consist of distinct subgroups with different trajectories of HRQL. The results of this study are encouraging given that only a small proportion of children can be considered at-risk for poor HRQL. Scarce health care resources should be allocated to this group of children. Although child behavior or cognitive problems were the strongest risk factors in the model, this study demonstrated that the family environment plays a substantial role in children's HRQL. This finding contrasts epilepsy-specific variables such as seizure type, frequency, and epilepsy severity that did not have a significant impact on children's HRQL. Given that family factors are modifiable, it is important that physicians in the pediatric neurology setting adopt family-centered care practices to potentially alter trajectories of HRQL in children to more favorable outcomes.

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Disclosure

None of the authors has any conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Adewuya AO. (2006) Parental psychopathology and self-rated quality of life in adolescents with epilepsy in Nigeria. *Dev Med Child Neurol* 48:600–603.

Austin JK, Risinger MW, Beckett LA. (1992) Correlates of behavior problems in children with epilepsy. *Epilepsia* 33:1115–1122.

Austin JK, Smith MS, Risinger MW, McNelis AM. (1994) Childhood epilepsy and asthma: comparison of quality of life. *Epilepsia* 35:608–615.

Austin JK, Perkins SM, Johnson CS, Fastenau PS, Byars AW, deGrauw TJ, Dunn DW. (2010) Self-esteem and symptoms of depression in children with seizures: relationships with neuropsychological functioning and family variables over time. *Epilepsia* 51:2074–2083.

Austin JK, Perkins SM, Johnson CS, Fastenau PS, Byars AW, deGrauw TJ, Dunn DW. (2011) Behavior problems in children at time of first recognized seizure and changes over the following 3 years. *Epilepsy Behav* 21:373–381.

Baca CB, Vickrey BG, Hays RD, Vassar SD, Berg AT. (2010) Differences in child versus parent reports of the child's health-related quality of life in children with epilepsy and healthy siblings. *Value Health* 13:778–786.

Baca CB, Vickrey BG, Vassar SD, Berg AT. (2012) Seizure recency and quality of life in adolescents with childhood-onset epilepsy. *Epilepsy Behav* 23:47–51.

Connolly AM, Northcott E, Cairns DR, McIntyre J, Christie J, Berroya A, Lawson JA, Bleasel AF, Bye AM. (2006) Quality of life of children with benign rolandic epilepsy. *Pediatr Neurol* 35:240–245.

Fastenau PS, Shen J, Dunn DW, Perkins SM, Hermann BP, Austin JK. (2004) Neuropsychological predictors of academic underachievement in pediatric epilepsy: moderating roles of demographic, seizure, and psychosocial variables. *Epilepsia* 45:1261–1272.

Ferro MA, Speechley KN. (2012) Depressive symptoms in mothers of children with epilepsy: a comparison of growth curve and latent class modeling. *Health Serv Outcomes Res Method* 12:44–61.

Ferro MA, Avison WR, Campbell MK, Speechley KN. (2010) Do depressive symptoms affect mothers' reports of child outcomes in children with new-onset epilepsy? *Qual Life Res* 19:955–964.

Ferro MA, Avison WR, Campbell MK, Speechley KN. (2011) The impact of maternal depressive symptoms on health-related quality of life in children with epilepsy: a prospective study of family environment as mediators and moderators. *Epilepsia* 52:316–325.

Hoare P, Mann H, Dunn S. (2000) Parental perception of the quality of life among children with epilepsy or diabetes with a new assessment questionnaire. *Qual Life Res* 9:637–644.

Human Resources and Skills Development Canada (HRSDC). (2013) *Canadians in context – households and families*. Human Resources and Skills Development Canada (Ed.). Government of Canada, Ottawa, ON.

Jakovljevic MB, Jankovic SM, Jankovic SV, Todorovic N. (2008) Inverse correlation of valproic acid serum concentrations and quality of life in adolescents with epilepsy. *Epilepsy Res* 80:180–183.

Law M, Hanna S, King G, Hurley P, King S, Kertoy M, Rosenbaum P. (2003) Factors affecting family-centred service delivery for children with disabilities. *Child Care Health Dev* 29:357–366.

McCubbin HI, Thompson AI, McCubbin MA. (1996a) FILE: family inventory of life events and changes. In McCubbin HI, Thompson AI, McCubbin MA. (Ed.) *Family assessment: resiliency, coping and adaptation. Inventories for research and practice*. University of Wisconsin Publishers, Madison, WI, pp. 103–145.

McCubbin HI, Thompson AI, McCubbin MA. (1996b) FIRM: family inventory of resources for management. In McCubbin HI, Thompson AI, McCubbin MA. (Ed.) *Family assessment: resiliency, coping and adaptation. Inventories for research and practice*. University of Wisconsin Publishers, Madison, WI, pp. 307–323.

Miller V, Palermo TM, Grewe SD. (2003) Quality of life in pediatric epilepsy: demographic and disease-related predictors and comparison with healthy controls. *Epilepsy Behav* 4:36–42.

Modi AC, Ingerski LM, Rausch JR, Glauser TA. (2011) Treatment factors affecting longitudinal quality of life in new onset pediatric epilepsy. *J Pediatr Psychol* 36:466–475.

Nagin DS. (2005) *Group-based modeling of development*. Harvard University Press, Cambridge.

Oostrom KJ, Smeets-Schouten A, Kruitwagen CL, Peters AC, Jennekens-Schinkel A, Dutch Study Group of Epilepsy in C. (2003) Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only"–a prospective, longitudinal, controlled study starting at diagnosis. *Pediatrics* 112:1338–1344.

Oostrom KJ, van Teeseling H, Smeets-Schouten A, Peters AC, Jennekens-Schinkel A. (2005) Three to four years after diagnosis: cognition and behaviour in children with 'epilepsy only'. A prospective, controlled study. *Brain* 128:1546–1555.

Patient-Centered Outcomes Research Institute (PCORI). (2012) *Methodology report*. Patient-Centered Outcomes Research Institute, Washington, DC.

Perucca E, Gram L, Avanzini G, Dulac O. (1998) Antiepileptic drugs as a cause of worsening seizures. *Epilepsia* 39:5–17.

Pignone MP, Gaynes BN, Rushton JL, Burchell CM, Orleans CT, Mulrow CD, Lohr KN. (2002) Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 136:765–776.

Radloff LS. (1977) The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1:385–401.

Rodenburg R, Meijer AM, Dekovic M, Aldenkamp AP. (2005) Family factors and psychopathology in children with epilepsy: a literature review. *Epilepsy Behav* 6:488–503.

Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. (2000) Validation of a new quality of life measure for children with epilepsy. *Epilepsia* 41:765–774.

Sabaz M, Cairns DR, Lawson JA, Bleasel AF, Bye AM. (2001) The health-related quality of life of children with refractory epilepsy: a comparison of those with and without intellectual disability. *Epilepsia* 42:621–628.

Sabaz M, Lawson JA, Cairns DR, Duchowny MS, Resnick TJ, Dean PM, Bye AM. (2003) Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. *Epilepsy Behav* 4:680–691.

Sherman EM, Slick DJ, Connolly MB, Eyrl KL. (2007) ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. *Epilepsia* 48:1083–1091.

Smilkstein G. (1978) The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract* 6:1231–1239.

Smilkstein G, Ashworth C, Montano D. (1982) Validity and reliability of the family APGAR as a test of family function. *J Fam Pract* 15:303–311.

Smith L, Coleman V, Bradshaw M. (2002) *Family-centred care. Concept, theory and practice*. Palgrave, New York.

Speechley KN, Levin SD, Wiebe S, Blume WT. (1999) Referral patterns of family physicians may allow population-based incidence studies of childhood epilepsy. *Epilepsia* 40:225–231.

Speechley KN, Sang X, Levin S, Zou GY, Eliasziw M, Smith ML, Camfield C, Wiebe S. (2008) Assessing severity of epilepsy in children: preliminary evidence of validity and reliability of a single-item scale. *Epilepsy Behav* 13:337–342.

Speechley KN, Ferro MA, Camfield CS, Huang W, Levin SD, Smith ML, Wiebe S, Zou G. (2012) Quality of life in children with new-onset epilepsy: a 2-year prospective cohort study. *Neurology* 79: 1548–1555.

Taylor J, Jacoby A, Baker GA, Marson AG. (2011) Self-reported and parent-reported quality of life of children and adolescents with new-onset epilepsy. *Epilepsia* 52:1489–1498.

Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, Wit JM. (1998) The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 7:387–397.

van Empelen R, Jennekens-Schinkel A, van Rijen PC, Helders PJ, van Nieuwenhuizen O. (2005) Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. *Epilepsia* 46:258–271.

von Lehe M, Lutz M, Kral T, Schramm J, Elger CE, Clusmann H. (2006) Correlation of health-related quality of life after surgery for mesial temporal lobe epilepsy with two seizure outcome scales. *Epilepsy Behav* 9:73–82.

Williams J, Steel C, Sharp GB, DelosReyes E, Phillips T, Bates S, Lange B, Griebel ML. (2003) Parental anxiety and quality of life in children with epilepsy. *Epilepsy Behav* 4:483–486.

Wood LJ, Sherman EM, Hamiwka LD, Blackman MA, Wirrell EC. (2008) Maternal depression: the cost of caring for a child with intractable epilepsy. *Pediatr Neurol* 39:418–422.

Wyrwich KW, Tierney WM, Wolinsky FD. (1999) Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol* 52:861–873.

Yong L, Chengye J, Jiong Q. (2006) Factors affecting the quality of life in childhood epilepsy in China. *Acta Neurol Scand* 113:167–173.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Details of statistical analysis.

Table S1. Trajectory-wise distribution of participants for children with and without complete follow-up.