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Emotional Well-Being in Children with New-Onset Epilepsy

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Abstract

Research suggests increased risk for adverse psychosocial outcomes and poor health-related quality of life and emotional well-being (EWB) in children with epilepsy compared to their healthy peers. The factors associated with poor EWB and the course of EWB in these children remains unclear. The objectives of this study were to: investigate the relationship between epilepsy-related and family factors and children's EWB two years after the diagnosis of epilepsy; identify the average group trajectory of EWB in children with newly-diagnosed epilepsy over the first two years; and investigate whether we can identify subgroups of children with epilepsy that can be better represented with yet unidentified unique trajectories to describe their course of EWB, rather than using a single homogeneous group trajectory to represent all children.

Data came from a multi-centre prospective cohort study of children with newly-diagnosed epilepsy from across Canada (Health-Related Quality of Life in Children with Epilepsy Study; HERQULES, n=373). EWB was measured using the Quality of Life in Childhood Epilepsy Questionnaire. Multiple regression assessed the relationship between epilepsy-related factors and EWB and tested possible mediation or moderation effects of family factors. Latent growth modeling and multinomial logistic regression was used to identify trajectories of EWB, the factors associated with each trajectory, and predictors of group membership to a particular trajectory.

Behavioural problems, family functioning, family demands, and family resources were associated with poor EWB two-years post-diagnosis. Parental depressive symptoms were partially mediated by family functioning and by family demands. Family resources played a dual mediator/moderator role, moderating the relationship between severity of epilepsy and EWB.
Two linear trajectories were identified, with the same set of factors associated with baseline EWB for both trajectories, but factors differed in their association with EWB across time for the two trajectories. The level of severity of epilepsy and family resources predicted a child's membership to a particular trajectory.

Poor EWB in children with epilepsy is associated with several epilepsy-related and family factors. After a diagnosis of epilepsy, family factors appear to be the most important influences on changes in EWB over time so efforts to strengthen the family environment may warrant attention.

Keywords

Emotional well-being, children with epilepsy, childhood epilepsy, growth trajectories, family environment, longitudinal study

Co-Authorship Statement

For this doctoral dissertation and each of the manuscripts contained within, Shane William Goodwin played the primary role of creating the research questions, carrying out analyses, and the writing of all components, under the supervisory guidance of Dr. Kathy Nixon Speechley. The author's supervisor, Dr. Kathy Nixon Speechley, and committee members, Dr. Piotr Wilk and Dr. M. Karen Campbell provided ongoing contributions in the form of regular feedback and methodological advice throughout the research. This dissertation used data obtained from the Health-related Quality of Life in Children with Epilepsy Study (HERQULES) led by Dr. Kathy N. Speechley. Shane William Goodwin was the primary author of each manuscript.

Dedication

For Nathalie- my wife and best friend.
Thank you for your support and unconditional love.

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Table of Contents

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AEDs	Anti-epileptic Drugs
APGAR	Family Adaptability, Partnership, Growth, Affection, and Resolve
BIC	Bayesian Information Criteria
BLRT	Bootstrap Likelihood Ratio Test
CES-D	Centre for Epidemiological Studies Depression Scale
CFI	Comparative Fit Index
EWB	Emotional Well-Being
FILE	Family Inventory of Life Events & Changes
FIRM	Family Inventory of Resources for Management
GASE	Global Assessment of Severity of Epilepsy
HERQULES	Health-Related Quality of Life in Children with Epilepsy study
HRQL	Health-Related Quality of Life
LMR-LRT	Lo-Mendell-Rubin Likelihood Ration Test
MeSH	Medical Subject Headings
ML	Maximum Likelihood
MLR	Maximum Likelihood with Robust Standard Errors
RMSEA	Root Mean Square Error of Approximation
SRMR	Standardized Root Mean Residual
QOLCE-55	Quality of Life in Childhood Epilepsy, 55-item version

Chapter One: Introduction and Research Objectives

1.1 Overall Goal

The goal of this thesis research was to improve understanding of emotional well-being (EWB) in children with newly-diagnosed epilepsy as a step towards developing interventions to optimize children's health-related quality of life. Specifically, this research aimed to identify the course of EWB in children with newly-diagnosed epilepsy and identify predictors of poor EWB. It also aimed to further our understanding of the relationships among epilepsy-related factors and family factors by assessing a possible mechanism to describe their impact on EWB over a two-year period.

1.2 Background: An Introduction to Epilepsy

Epilepsy is a neurological disease and is defined as having at least one of the following conditions occur: "1) at least two unprovoked (or reflex) seizures occurring at least 24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; 3) diagnosis of an epilepsy syndrome"[1]. Seizures are intermittent states of irregular brain activity in which neurons in the brain have an increased predisposition of excitability resulting in alterations in both mood and behaviour. Increased firing of neurons can produce dramatic behavioural responses, changes to moods, and increased burdens on the individual[2]. Seizures are external manifestations of an underlying brain

abnormality, and the cause may be known or unknown, and have a single or multiple causes. It is estimated that 55-75% of seizures are from unknown causes[3]. The type of epilepsy is defined by the origin of the seizure as well as the cause of epilepsy. Seizures can be described as generalized, originating at a single point but quickly propagating to multiple points in the brain, or focal, where the seizure originates and stays in a location or hemisphere[4,5]. Generalized seizures, due to the occurrence across multiple locations, produce dramatic alterations to the individual, such as in tonic-clonic seizures where the skeletal muscles tense, consciousness is reduced, and convulsions begin, or in absence seizures where impairment to consciousness is the primary characteristic[4,5]. Due to the localized response, focal or partial seizures, produce sensory or motor disruption unique to the system being affected[4,5]. In symptomatic epilepsy, the underlying cause is known while for individuals diagnosed with idiopathic epilepsy, the underlying cause is unknown[4,5]. Causes of epilepsy can range from genetic defects or mutations to structural-metabolic abnormalities such as head injuries or central nervous system infections[4,5].

Epilepsy is the most common disease of the brain in children, with the incidence of epilepsy in children from developed countries reported as 40-60 cases per 100,000 per year[6-10] and worldwide the prevalence of epilepsy in children is estimated at 10.5 million[9]. In Canada, the incidence has been reported to be 41 cases per 100,000 per year[10] while the prevalence in children under age 15 is estimated to be between 2.5-4.4 per 1000[11]. Treatment for epilepsy typically involves drug therapy with one or more antiepileptic drugs (AEDs) and/or changes to diet such as

the inclusion of a ketogenic diet to reduce the number of seizures. In children with uncontrollable epilepsy, also known as intractable epilepsy, surgery may be an option, where 58-78% of patients undergoing hemispherectomy are reported to be seizure free post-surgery[12,13].

Children with epilepsy have a good clinical prognosis and approximately 80% of children with idiopathic epilepsy become seizure-free, and approximately 60% will discontinue medication two years post-diagnosis, with relatively low risks of relapse[14-16]. Across all types of epilepsy, approximately one-third will become seizure-free and discontinue medication[17]. However, even individuals who become seizure-free can have persisting psychosocial issues and increased burdens compared to healthy children. Children with epilepsy have more behavioural problems and mental health issues compared to healthy children. More specifically, children with epilepsy have an increased risk of conduct disorders, hyperactivity, aggression and anger, social issues, poorer self-esteem, and are more likely to be diagnosed with a psychiatric problem compared to healthy children[18-22]. Psychiatric disorders have been found in 29-58% of children with epilepsy compared to a prevalence of 7% in the general population[18,23], and emotional disorders (16%) have been estimated as four times higher in children with epilepsy compared to the general population (4.2%)[18].

The issues that children with epilepsy experience are not limited to psychosocial problems but extend into other areas of life including cognition, where children with epilepsy are at increased risk for learning disorders, memory issues, and have lower IQ scores compared to healthy children[24,25]. Health-related quality of

life (HRQL) is poorer in children with epilepsy compared to their peers, and this continues to be true regardless of whether the comparison is to healthy children or children with asthma or diabetes[24,26]. While HRQL improves over time after diagnosis, it continues to be lower than healthy children two-years later[27].

1.3 An Introduction to Emotional Well-Being

The World Health Organization suggests operationalizing health as a multidimensional construct, defining it as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[28]. Mental well-being, relabelled as emotional well-being to remove any connection to mental health problems, is a balance between positive affects and negative affects, where affects are defined as moods and emotions that act as representations of people's evaluation of life events[29]. An individual is identified as having good emotional well-being by the presence of positive affects while having minimal negative affects.

EWB is one domain of HRQL and describes the emotional and psychological impact of a disease or disorder on an individual's overall health. EWB provides an opportunity to examine the broad emotional and psychological impact of a disease or disorder on an individual's overall health. EWB is often measured using one subscale HRQL instruments or by using multiple instruments measuring specific components. EWB is captured by items or subscales measuring depression, anxiety, self-esteem, hopelessness/helplessness, emotional distress, and items measuring positive affect including happiness or confidence. These measures assess the impact a disease or its treatment has on how an individual feels and functions during

everyday life[30]. The assessment of EWB presents theoretical and practical challenges due to the difficulty in assessing emotional states independent of physical illness[31-33]. One issue is that affective and somatic states are often not independent of one another[33] and measures that include items measuring somatic symptoms may result in biased estimates of EWB. A second challenge in the measurement of EWB is that it is a multidimensional construct, defined as a balance between the presence of positive affect and the absence of negative affect[29], but in practice, EWB is often operationalized using only negative affect items. The consequence of this discrepancy between construct and measurement has not been investigated.

1.4 Objectives

The specific objectives of this thesis are to:

1. Investigate the relationship between epilepsy-related and family factors and children's EWB two years after the diagnosis of epilepsy.
    a. Do baseline epilepsy-related or family factors predict EWB two years post-diagnosis?
    b. Do baseline family functioning or family demands mediate the relationships between baseline epilepsy-related factors and the EWB two years post-diagnosis?
    c. Do baseline family resources moderate the relationship between baseline epilepsy-related factors and EWB two years post-diagnosis?

   d. Is there a significant difference in estimates of EWB obtained when measuring EWB using a negative-only item operationalization?
   e. Does the set of predictors found previously, remain the same in both direction and magnitude when using the two different definitions of EWB?

2. Identify the average group trajectory of EWB in children with newly-diagnosed epilepsy over the first two years and examine the extent to which there is statistically significant variability around the average. Specifically,
   a. What is the level of EWB at baseline?
   b. How does EWB change as a function of time?
   c. How much variability exists across children in the level of EWB at baseline? How much variability exists across children in the rate of change in EWB across time?
3. Investigate whether we can identify subgroups of children with epilepsy that can be better represented with yet unidentified unique trajectories to describe their course of EWB, rather than using a single homogenous group trajectory to represent all children. Specifically;
   a. Is there significant unexplained variation for the average group trajectory? Can unique groups of children with epilepsy be identified that display significantly different trajectories than the average group trajectory?

b. If any groups are identified, what baseline epilepsy-related and family factors account for differences in the level of baseline EWB and the rate of change in EWB found among trajectories?
c. If any groups are identified, what baseline epilepsy-related and family factors are associated with group membership to the distinct trajectories?

1.5 What This Research Adds

This thesis research addresses a gap in knowledge on EWB in children with epilepsy. There is no currently published research examining EWB as a *process* to identify how these children are changing across time and how epilepsy and family factors may impact EWB over time. Very few studies have examined predictors of EWB in children and those that have provide mixed results across studies. This doctoral research follows an approach of treating each child as a unique and who may a distinct impact of a diagnosis of epilepsy. It is hoped that this research betters our understanding of the differences among children and the factors that explain them.

Finally, this study is unique as it examines EWB using a multidimensional perspective, focusing on the importance of including both positive and negative items in the measurement of EWB. Given that a deficit-based approach is often used in childhood epilepsy, where examinations of mental health focus primarily on negative affect items, distinctions among individuals may be missed. This research

hopes to clarify the implications of including positive affect items in the measurement of emotional well-being.

1.6 How This Dissertation is Structured

This thesis research uses an integrated-article format, with each chapter representing a separate component. Chapter 2 provides systematic review on EWB in children with epilepsy and possible epilepsy-related and family factors that have been examined for their association with EWB. Chapter 3 presents the conceptual framework that forms the underlying guidance for all research objectives. The next three chapters, Chapters 4 through 6, present articles examining: methodological work on the primary measure used to obtain estimates of EWB (Chapter 4), describing the assessment and results for Objective 1 (Chapter 5), and Objectives 2 and 3 (Chapter 6). Finally, Chapter 7 presents conclusions and summarizes the overall findings of previous chapters and discusses implications, limitations, and steps moving forward. The appendices present details regarding data collection, measurement, instruments used, and data analysis methods, and serve to provide further information relevant across chapters to reduce repetition within chapters.

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Chapter Two: Emotional Well-Being in Children with Epilepsy: A Review of the Literature

2.1 Overview of Emotional Well-Being

Emotional well-being (EWB) is a multidimensional psychological construct and is one of the domains of health-related quality of life (HRQL), functioning to describe an individual's overall emotional state. EWB is described as a balance between positive affects and negative affects, where affects are moods and emotions that represent individual evaluations of life events[1]. Using this definition, EWB represents the overall impact of multiple components of mental health, such as depression, anxiety, self-esteem, satisfaction, confidence, and happiness[1]. Assessing EWB provides an opportunity to examine the broad psychological impact of a disease or disorder on overall health.

Poor EWB has been found to be associated with an increased risk of adverse outcomes in the general population such as an increased risk of cardiovascular disease after major life events and increased susceptibility to viral infections, suggesting EWB may modify the stress response that in turn can increase susceptibility to physical illness[2,3]. There is some evidence from research on chronic disorders that poor EWB during childhood may affect emotional growth during development, with persisting effects in adulthood[4].

Epilepsy is one of the most common chronic neurological conditions in children and is associated with increased risk of poor HRQL[5-6]. Evidence suggests that children with epilepsy tend to have worse psychological functioning compared

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to other children; specifically, children with epilepsy are at increased risk for emotional and behavioural problems, depression, anxiety, social incompetence, hyperactivity, aggression and anger, poorer self-esteem, and diminished family functioning, with effects extending into adulthood[7-12]. The Isle of Wight study, a major cohort study conducted in 1970, identified that children with epilepsy had an increased prevalence of psychiatric disorders (29-58%) compared to the general population (7%)[13]. A more recent study estimated the prevalence of psychiatric disorders in children with epilepsy to be 37% (95% CI: 22-49%)[14].

The increased risk of psychiatric disorders in children with epilepsy stresses the importance of identifying risk factors associated with EWB, as interventions targeting risk factors for poor EWB may provide the opportunity to improve the child's overall HRQL. Currently, this knowledge is not well described in the literature. The aim of this article is to: (1) critically examine the quality of research investigating EWB in children with epilepsy and (2) to identify factors associated with EWB.

2.2 Methodology

2.2.1 Search Strategy

In October 2016, the electronic databases MEDLINE and PsychINFO were searched for articles investigating EWB in children with epilepsy. EWB in all searches was defined as being the combination of positive and negative affect. Combinations of keywords included the following: adolescent, child, childhood epilepsy, emotional well-being, subjective well-being, emotional distress, psychosocial well-being. The search strategy provided a list of medical subject

headings (MeSH) that were exploded to ensure a broad search of relevant studies. MeSH were used to provide a hierarchical search regarding all articles relevant to EWB in childhood epilepsy, details of which can be found in Table 2-1. For articles deemed relevant, the ancestry method of reviewing references was used to identify further studies that may have been missed by the previous search strategy. Finally, Web of Science was used to identify any articles found cited within previously found articles. These articles were then reviewed to identify any additional articles. The search results at each step of the search strategy can be found in Figure 1.

2.2.2 Inclusion Criteria

To be included in this review, a study needed to: (1) measure EWB using multidimensional quality of life measures that include an EWB domain, use a single measure of EWB, or measure three or more components of EWB; (2) include children with epilepsy up to 18 years of age; and (3) be written in the English language. Articles were excluded if: (1) the focus was to develop or validate a measure of EWB; (2) the target population was not children with epilepsy; (3) the focus was to report on an intervention for children with epilepsy; (4) the focus was to examine children with multiple co-morbidities, of which epilepsy was only one of multiple diseases or disorders, with epilepsy results not presented separately; (5) they focused on a review of quality of life methodology; and (6) they only measured one or two components of emotional well-being.

2.2.3 Assessment of Study Quality

All articles were evaluated using a modified version of the Quality Index[15]. The Quality Index was developed to evaluate the quality of both randomized and non-randomized intervention studies and has been shown to be valid and reliable[15-18]. The 15-item modified version was used as it excludes items specific to intervention studies such as randomization and blinding and can be found in Table 2-2. Each item is dichotomously scored as 0 or 1 (no or yes) providing a maximum score of 15, with higher scores indicating better methodological quality. The Quality Index contains three subscales: reporting, external validity, and internal validity. A single item is included to assess the statistical power of the study.

2.3 Results

The 26 studies reviewed report research spanning 26 years, from 1990 to 2016. The results reflect a global perspective with studies from United States of America (4), Australia (3), Norway (3), United Kingdom (4), Canada (3), China (3), Poland (2), France (1), Japan (1), Iran (1), and Nigeria (1). Sixteen measures were used to assess EWB: the Strengths and Differences Questionnaire[19]; Rutter Scale[20]; Child Behaviour Checklist[21]; Piers Harris Children's Self-Concept Scale[22]; Quality of Life in Childhood Epilepsy Questionnaire[23]; The Behavior Assessment System for Children[24]; Youth Quality of Life Instrument[25]; Multidimensional Anxiety Scale for Children[26]; Child Depression Inventory[27]; Child Health Questionnaire[28]; Beck Youth Inventories for Emotional and Social Impairment[29]; Pediatric Quality of Life Inventory[30]; Quality of Life Inventory for Adolescents[31]; KINDL[32]; Moods and

Feelings Questionnaire[33]; KIDSCREEN[34]. Two studies did not use a validated scale of EWB but rather asked children a series of individual questions relating to their EWB or conducted an open-ended interview with children and later categorized these discussions based on the words invoked such as fears, worries, or satisfactions[35,36]. The 22 studies had a median modified Quality Index score of 9, ranging from 6-13. The median subscale scores were 5 (range, 3-7) for reporting; 1 (range, 0-3) for external validity; and 3 (range, 1-3) for internal validity. Only one study reported a formal sample size or power calculation[35]. A median score of 9 suggests that results of the study are considered modest in quality. All studies included were found to be exclusively cross-sectional in design.

Table 2-3 highlights the key features of each study. The 22 studies had multiple objectives: twelve compared EWB among children with and without epilepsy[37-46,58-59], seven comparing children with epilepsy to healthy children[37-41,58-59] and six comparing children with epilepsy to children with other chronic conditions[42-46,58]. Fourteen studies investigated predictors of EWB[37-38,43,46-55,57]. Three studies reported the characteristics of their sample but made no comparisons or predictions[35,36,56].

2.3.1 Estimates of Emotional Well-Being

Twelve studies reported that EWB was poorer in children with epilepsy compared to both healthy children and to children with other chronic conditions (see Table 2-4). Due to differences in the measurement of EWB, it is difficult to make direct comparisons across studies, but generally, the effect is consistent in direction.

Studies vary in terms of whether these differences are statistically significant, with not all studies reaching the significance threshold.

2.3.2 Factors Associated with Emotional Well-Being

The studies included identified several epilepsy-related, family, and sociodemographic factors to be associated with EWB in children with epilepsy. Factors associated with poor EWB include the presence of learning difficulties[54], comorbidity[51], early age of onset[53], poor leadership skills[53], depressive symptoms[53], withdrawal[53], more severe seizures[43,52], gender (girls having more internalizing problems while boys having increased risk of externalized behavioural problems)[37,43,52], lateralization differences in the brain[50], and symptomatic epilepsy[48].

Not all associations are well established, with some studies suggesting non-significant associations, particularly with gender[38,51,54] and severity of seizures[47,55]. Seizure type and seizure duration (longer durations) were significant in univariable analysis, but once entered into a stepwise regression, the associations were non-significant[55]. Significant associations found in univariable analyses became non-significant in later analyses for several other factors: economic resources[55], maternal education[55], number of anti-epileptic drugs(AEDs)[52,54], duration of epilepsy[54], and age of onset[54]. Two studies found the association between increased number of AEDs, lateralization differences, and increased frequency of seizures with EWB to be non-significant but did not indicate whether the factors were previously found significant in univariable analyses[46,47]. It is unknown whether additional

factors have been examined for their association with EWB but not reported in publications due to negative results.

2.4 Discussion

This review suggests that EWB is poorer in children with epilepsy compared to both healthy children and children with other co-morbidities, particularly asthma. The studies included in this review were all cross-sectional in either design or analysis, limiting discussions to that of associations instead of prediction or causality. Not all studies assessed EWB at the onset or provide a timeframe for the onset of epilepsy. Different factors may have larger effects at different stages of a child's life post-diagnosis, where we would expect the burden of epilepsy placed on the child and family would be highest near the time of diagnosis. As a child and the family adapt to a diagnosis of epilepsy, the effects of a particular factor may change, and these changes could be missed by the reviewed studies. The lack of longitudinal studies makes it difficult to assess possible mechanisms to explain the relationship between factors and EWB and in capturing any dynamic effects across time. None of the studies attempt to explain possible mechanisms for why a particular factor would be associated with EWB or attempts to identify key targets for intervention to improve EWB in childhood epilepsy.

The studies reviewed provide a groundwork that future studies should work to clarify. By using more robust study designs and methods, future studies can clarify some of the inconsistencies identified. In doing so, studies will better address many of the limitations found in the included studies. These limitations will be

discussed below and can be grouped into the following categories: reporting, external validation, internal validation, and power.

2.4.1 Reporting

All studies included in this review employed cross-sectional study designs or conducted cross-sectional analyses. Use of cross-sectional design limits the interpretation of results and does not adequately disentangle inconsistent results found across studies. No causal inferences can be made, and caution should be taken in interpreting results due to the inability to establish temporality; however, these studies can guide the inclusion of variables in future studies. The reporting subscale of the modified Quality Index indicated that studies were relatively good regarding their ability to report relevant information to the reader. A limitation of nearly all studies was a lack of reported response rate. Such information allows the reader to understand the sample in the study. A poor response rate can be an indication of a sampling bias if nonresponse is unequal between groups or associated with either exposure or outcome, and the response rate is often used to gauge the overall quality of the study. Poor response rates provide difficulties in generalizing results, as differences may exist between those responders and nonresponders.

2.4.2 External Validity

External validity, as measured by the modified Quality Index[15] was low among the included studies. A major limitation was the inclusion of a single centre, typically for tertiary care, which may lead to a very specific population of children, and not necessarily representing the full range of children with epilepsy. It is

unlikely that a probability-based sampling method could be employed. Not all studies included used only a single centre, with several studies using multiple hospitals, schools, or a limited number of referral centres. These studies are likely better able to generalize results to the general population of children with epilepsy.

2.4.3 Internal Validity

Internal validity was found to be adequate in this review, with the primary limitation being a lack of inclusion of confounders. Adequate control of confounders is important in the estimation of associations between factors and EWB. Studies did not adequately control potential confounders and often did not mention whether analyses were being controlled or adjusted for a set of variables. Automated regression methods were used in one of the studies examined, which may result in the exclusion of important factors that should be included in the final model. Ideally, models should be constructed based on a conceptual model, providing theory-driven results rather than data-driven results. Not all studies used robust methods for estimating associations, and it was not always clear whether adjustments for multiple comparisons were made. Without the adjustment for multiple comparisons, there will be a greater chance of type-I errors. The mode of survey results was mixed including parental reporting, child reporting, and teacher reporting. While each of these provides a different perspective on the perception of the child's EWB, it makes comparisons among the studies difficult, as it is unknown whether differences result in differences in reporting.

2.4.4 Power

Only one study reviewed reported sample size calculations[35]. It may be the case that inadequate sample sizes limited some of the studies and could explain some inconsistent findings across studies.

2.5 Conclusion

As a whole, the studies reviewed demonstrate that children with epilepsy have poorer EWB compared to healthy children and children with other comorbidities. Our review suggests that multiple factors are associated with EWB in children with epilepsy. There is room for improvement, particularly in conducting more longitudinal research, including confounders, and consistently measuring EWB. These improvements would provide more comparable estimates of the relationship between potential factors and children's EWB. None of the studies reviewed assessed the role of family factors, which have been found to be important in their association with overall health-related quality of life in children[61]. Future work should focus on identifying amenable factors, examining the role of family factors on EWB, and how to incorporate these factors into interventions to improve EWB in children with newly diagnosed epilepsy.

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Table 2-1. Detailed Search Strategy using OVID system.

1. adolescent OR child
2. epilepsy OR childhood epilepsy
3. personal satisfaction OR quality of life
4. emotions OR mental health
5. #1 AND #2
6. #3 OR #4
7. #5 AND #6

Table 2-2. The Modified Quality Index.

Reporting
1. Is the hypothesis/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the main findings of the study clearly described?
5. Does the study provide estimates of the random variability in the data for the main outcome?
6. Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?
7. Is the response rate clearly described?
External Validity
8. Were the patients asked to participate in the study representative of the entire population from which they were recruited?
9. Were patients who were prepared to participate representative of the entire population from which they were recruited?
10. Were the staff, places, and facilities where the patients were studied, representative of the treatment the majority of patients receive?
Interval Validity
11. If any of the results of the study were based on "data dredging," was this made clear?
12. Were the statistical tests used to assess the main outcomes appropriate?
13. Were the main outcome measures used valid and reliable?
14. Was there adequate adjustment in the analyses from which the main results were drawn
Power
15. Did the study provide a sample size or power calculation to detect important effects where the probability value for a difference being due to chance is less than 0.05?

Table 2-3. Summary of studies included in review.

Citation	Study Design	Sample	Measure	Focus of Study	Quality Index Score (of 15)
Elliott et al. (Canada)[35]	Cross-sectional	N=49 Tertiary-care hospital for children Refractory seizures Mean age: 13.6 years	Semi-structured, open-ended interview to describe emotions children are feeling	Descriptive Study	7 of 9
Yu et al. (China)[36]	Cross-sectional	N=555: n=258 children n=297 adolescents 21 hospitals across China Mean age (Children): 8.6 years Mean age (Adolescents): 15.9 years	Self-created questionnaire to describe the characteristics of the population	Descriptive Study	8
Alfstad et al. (Norway)[37]	Cross-sectional	N=13,674: n=110 epilepsy n=13,564 controls Schools in Akershush, Norway Age ranges: 8-13 years	SDQ	Comparison of groups; Factors associated with outcome	12
Hanssen-Bauer et al. (Norway)[38]	Cross-sectional	N=10,809: n= 74 epilepsy n= 297 British outpatient sample n=10,438 British norms Referral centre Age ranges: 8-13 years	SDQ	Comparison of groups; Factors associated with outcome	9

Citation	Study Design	Sample	Measure	Focus of Study	Quality Index Score (of 15)
Lossius et al. (Norway)[39]	Cross-sectional	N=8467: n=130 epilepsy n=8,337 controls 65 schools across Norway Mean age (epilepsy): 15.1 years Mean age (controls): 15.0 years	SDQ	Comparison of groups	12
Tanabe et al. (Japan)[40]	Cross-sectional	n=83 epilepsy Primary care facility Japanese controls not described Mean age: 10.6 years	SDQ	Comparison of groups	7
Eddy et al. (UK)[41]	Cross-sectional	N=152: n=50 epilepsy n=102 controls Epilepsy: referred to clinic. Controls: school recruitment Mean age (epilepsy): 12.2 years Mean age (controls): 13.1 years	YQOL-R CBCL CDI MASC	Comparison of groups	7
Austin et al. (USA)[42]	Cross-sectional	N=253: n=129 epilepsy n=124 asthma Outpatient clinics and private physicians Mean age (epilepsy): 10.5 years Mean age (asthma): 10.2 years	CBCL CSCS	Comparison of groups	9

Citation	Study Design	Sample	Measure	Focus of Study	Quality Index Score (of 15)
Austin et al. (USA)[43]	Cross-sectional	N=228: n=117 epilepsy n=111 asthma Outpatient clinics and private physicians Mean age (epilepsy): 10.5 years Mean age (asthma): 10.2 years	CBCL CSCS	Comparison of groups; Factors associated with outcome	10
Hamiwka et al. (Canada)[44]	Cross-sectional	N=98: n=49 seizure group n=18 non-seizure group n= 31 clinical norms Referral centre Clinical norms and healthy norms obtained from CHQ manual Mean age (seizure): 11.2 years Mean age (non-seizure): 10.9 years	CHQ	Comparison of groups	12
Taylor et al. (UK)[45]	Part of randomized trial	n=248 epilepsy Hospital outpatient clinics Control information from various studies Age range (epilepsy): 8-15 years	QOLIE-AD CHQ Rutter Scale KINDL-R	Comparison of groups	8

Citation	Study Design	Sample	Measure	Focus of Study	Quality Index Score (of 15)
Mathiak et al. (Poland)[46]	Cross-sectional	N=90: n=30 epilepsy n=60 controls Outpatient clinic Controls from a larger other study Mean age (epilepsy): 11.3 years Mean age (controls): 10.9 years	BYI	Comparison of groups; Factors associated with outcome	6
Sabaz et al. (Australia)[47]	Cross-sectional	N=94 Two tertiary referral units Refractory epilepsy Mean ages: 11.3-11.7 years, stratified by IQ	QOLCE	Factors associated with outcome	10
Sabaz et al. (Australia)[48]	Cross-sectional	N=115 Four tertiary paediatric centres Mean ages: 9.5-11.6 years, stratified by epilepsy type	QOLCE CHQ	Factors associated with outcome	11
Soria et al. (France)[49]	Cross-sectional	N=153 Five specialized institutions and four hospitals Mean age: 9.5 years	QOLCE	Factors associated with outcome	8

Citation	Study Design	Sample	Measure	Focus of Study	Quality Index Score (of 15)
Mathiak et al. (Poland)[50]	Cross-sectional	N=31 Outpatient clinic Mean age: 11.2 years	QOLCE	Factors associated with outcome	6
Modi et al. (USA)[51]	Cross-sectional	N=109 Tertiary care hospital Mean age: 8.2 years	PedsQL	Factors associated with outcome	9
Turky et al. (UK)[52]	Cross-sectional	N=30 37 general practices Mean age: 12.0 years	SDQ MFQ	Factors associated with outcome	13
Clary et al. (USA)[53]	Cross-sectional	N=132 Tertiary care hospital Mean age: 10.9 years	QOLCE BASC-2	Factors associated with outcome	7
Lagunju et al. (Nigeria)[54]	Cross-sectional	N=84 Referral centre Mean age: 10.6 years	Rutter Scale	Factors associated with outcome	12

Citation	Study Design or Analysis	Sample	Measure	Focus on Study	Quality Index Score (of 15)
Yong et al. (China)[55]	Cross-sectional	N=418 Outpatient clinic Mean age: 9.0 years	QOLCE	Factors associated with outcome	9
Connolly et al (Australia)[56]	Cross-sectional	N=30 Benign rolandic epilepsy Mean age: 9.7 years	QOLCE	Descriptive Study	8
Reilly et al. (UK)[57]	Cross-sectional	N=85 Postal district selection Mean age: 10.8 years	QOLCE	Factors associated with outcome	13
Mezgebe et al. (Canada)[58]	Cross-sectional portion of larger longitudinal study	N=6784 n=345 epilepsy n=489 cerebral palsy n=5950 general population Mean age (epilepsy): 9.9 years Mean age (cerebral palsy): 10.2 years Mean age (general): 9.7 years	KIDSCREEN	Factors associated with outcome Comparison of groups	11
Liu et al. (China)[59]	Cross-sectional	N=439 n=223 epilepsy n=216 healthy Outpatient clinic	QOLCE	Comparison of groups	8
Momeni et al (Iran)[60]	Cross-sectional	N=108 Mean age: 10.1 years Single private centre	QOLCE	Factors associated with outcome	8

Table 2-4. Emotional well-being comparing children with epilepsy to controls (healthy or children with other chronic illness)

Study	**Sample size and Comparison**	**Effect Estimate (means and standard deviations unless noted)**
Alfstad et al. (Norway)[37]	Epilepsy (n=110) Healthy Controls (n=13,564)	Emotional problems: 31.5% vs. 19.3% Conduct problems: 21.6% vs. 12.3%
Hanssen-Bauer et al. (Norway)[38]	Epilepsy (n=54) Unconfirmed Epilepsy (n=20) British Community Sample (n=5226 and n=5212 for girls and boys respectively)	*Epilepsy compared to Unconfirmed* Girls: Emotional problems: 6.0 (1.7) vs. 4.3 (2.9) Boys: Emotional problems: 3.7 (2.6) vs. 2.8 (3.4) Girls: Conduct problems: 2.1 (1.2) vs. 2.6 (1.7) Boys: Conduct problems: 3.1 (1.7) vs. 2.8 (1.6) *Higher scores indicate more problems *Epilepsy compared to British Community Sample:* Girls: Abnormal SDQ Emotion Score: 50% vs. 12.1% Boys: Abnormal SDQ Emotion Score: 35% vs. 10.7%
Lossius et al. (Norway)[39]	Epilepsy (n=130) Healthy Controls (n=8,337)	Emotional problems: 3.3 (2.5) vs. 2.6 (2.5) Conduct problems: 2.6 (2.5) vs. 2.2 (1.8) *Higher scores indicate more problems Abnormal SDQ Emotion Score: 24.6% vs. 11.4% (Norway cutoff)
Tanabe et al. (Japan)[40]	Epilepsy (n=83) Healthy Controls (n=2,899)	SDQ Emotional problems: 13.2-15.8% vs. 7.2-8.5% SDQ Conduct problems: 10.5-17.1% vs. 7.1-8.6%

Study	**Sample size and Comparison**	**Effect Estimate** **(means and standard deviations unless noted)**
Eddy et al. (UK)[41]	Epilepsy (n=50) Healthy Controls (n=102)	CDI: 8.0 (5.5) vs. 8.7 (8.7) MASC: 38.2 (14.9) vs. 33.3 (17.4) CBCL Total: 22.8 (17.5) vs. 10.8 (7.9) CBCL Internalizing: 8.7 (6.8) vs. 4.7 (3.4) CBCL Externalizing: 7.3 (7.5) vs. 2.0 (1.8) *Higher scores indicate poorer outcomes (increased depressive symptoms, anxiety, frequency of internalizing or externalizing problems) YQOL Self: 93.8 (20.0) vs. 101.2 (20.0) YQOL Environment: 82.2 (13.7) vs. 83.2 (11.5) *Lower scores indicate poorer outcomes
Austin et al. (USA)[42]	Epilepsy (n=129) Asthma (n=124)	CSCS Happiness and Satisfaction: 47.8 (11.6) vs. 52.0 (7.9) *Lower scores indicate less satisfaction and happiness CSCS Anxiety: 52.4 (10.4) vs. 47.7 (9.2) CBCL Internalizing: 61.9 (10.6) vs. 58.6 (11.4) CBCL Externalizing: 56.5 (10.3) vs. 52.4 (11.2) *Higher scores indicate poorer outcomes (increased anxiety, frequency of internalizing/externalizing problems)

Study	**Sample size and Comparison**	**Effect Estimate** **(means and standard deviations unless noted)**
Austin et al. (USA)[43]	Epilepsy (n=117) Asthma (n=111)	CSCS Happiness and Satisfaction: 8.3 (2.2) vs. 8.4 (1.9) *Lower scores indicate less satisfaction and happiness CSCS Anxiety: 9.9 (3.7) vs. 10.7 (3.2) CBCL Internalizing: 58.5 (11.2) vs. 53.2 (11.0) CBCL Externalizing: 55.0 (10.5) vs. 52.1 (11.3) *Higher scores indicate poorer outcomes (increased anxiety, frequency of internalizing/externalizing problems)
Hamiwka et al. (Canada)[44]	Seizure group (n=49) Non-Seizure group (n=18) Clinical epilepsy group (n=31)	*Parental report Seizure group compared to Clinical epilepsy group* CHQ Mental Health: 71.8 (17.6) vs. 75.9 (16.7) CHQ Self-Esteem: 72.7 (19.4) vs. 72.6 (24.7) *Parental report Seizure group compared to Non-seizure group* CHQ Mental Health: 71.8 (17.6) vs. 76.6 (15.9) CHQ Self-Esteem: 72.6 (24.7) vs. 90.1 (10.0) *Parental report Seizure group compared to CHQ Norm* CHQ Mental Health: 71.8 (17.6) vs. 79.7 (15.5) CHQ Self-Esteem: 72.6 (24.7) vs. 80.1 (19.1) *Lower scores indicate greater feelings of anxiety, depression, and dissatisfaction with life overall.

Study	**Sample size and Comparison**	**Effect Estimate** **(means and standard deviations unless noted)**
Taylor et al. (UK)[45]	Epilepsy (n=248) Healthy (n=1501) Asthma (n=254)	KINDL-R Emotional: 73.0 (18.1) vs. 83.0 vs. 82.4 KINDL-R Self-Esteem: 63.3 (22.4) vs. 66.6 vs. 63.7 *Lower scores indicate poorer emotional well-being and self-esteem
Mathiak et al. (Poland)[46]	Epilepsy (n=30) Controls (n=60)	BYI-Anxiety: 18.0-19.9 (7.0-12.2) vs. 17.4 (10.0) BYI-Depression: 14.3-14.5 (6.8-7.6) vs. 12.6 (8.0) BYI-Behaviour: 7.3-11.4 (4.0-10.2) vs. 7.1 (7.0) *Higher scores indicate poorer outcomes (increased anxiety, behavioural problems)
Mezgebe et al. (Canada)[58]	Epilepsy (n=345) Cerebral palsy (n=489) General population (n=5950)	*Self-reported Moods and Emotions:* 81.4 (16.3) vs. 85.5 (13.3) vs. 82.1 (15.3) *Proxy-reported Moods and Emotions:* 76.5 (13.6) vs. 85.3 (10.7) vs. 83.4 (12.4)
Liu et al. (China)[59]	Epilepsy (n=223) Controls (n=216)	QOLCE Depression 65.3 (19.4) vs. 82.3 (17.9) QOLCE Anxiety 62.3 (18.3) vs. 78.6 (23.7) QOCLE Control/Helplessness 61.5 (16.9) vs. 73.5 (13.8)

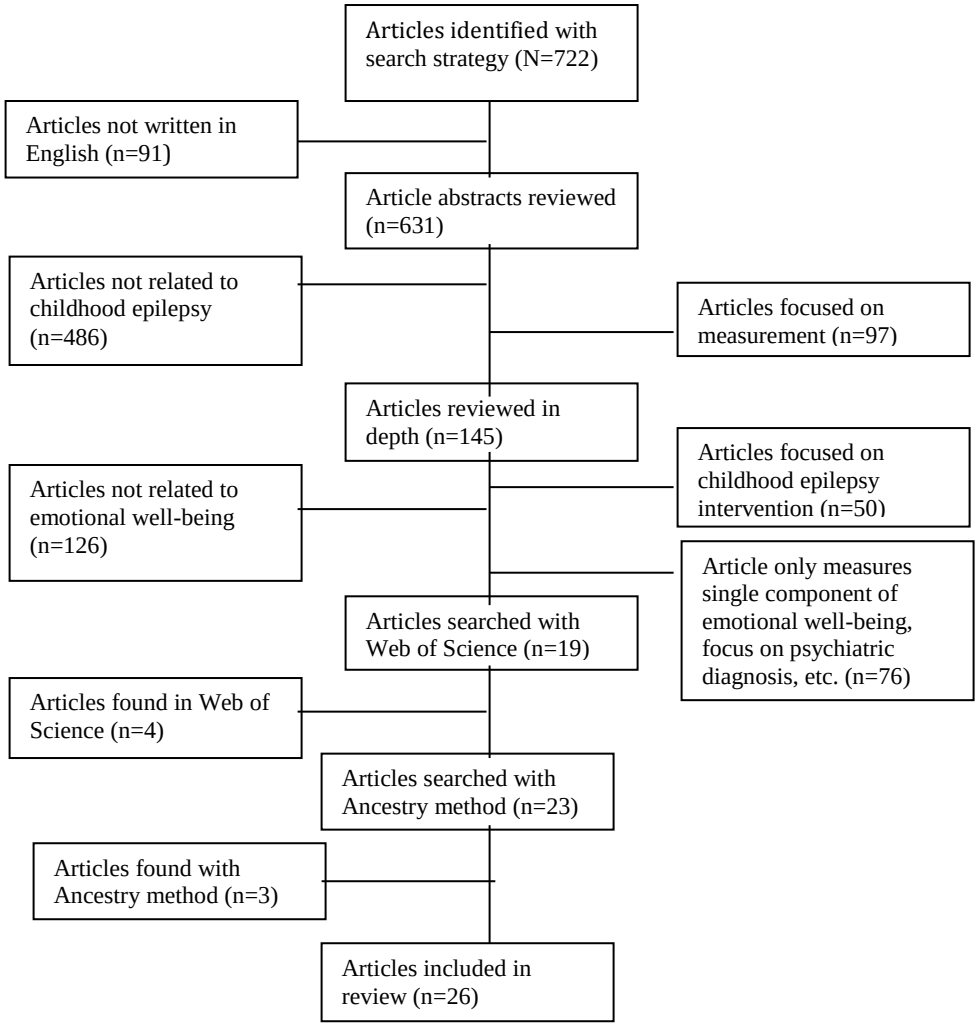

Figure 2-1. Schematic diagram of search strategy used to identify articles for review.

Chapter Three: Conceptual Framework

Physicians, researchers, and patients continue to be interested in research not only focused on physical symptoms of health but in domains contributing to overall health, such as emotional well-being (EWB). Interests in other domains of health continue to grow, in part, due to advances in medicine and technology resulting in impaired individuals living longer despite health problems. As individuals continue to live longer, optimizing their health-related quality of life (HRQL) and the domains that contribute to the construct become important foci. Thus, our attention must shift to investigating potential pathways to optimal health, where the effects of multiple factors determine an individual's overall health. A significant effort is required to find an avenue for targeted therapies to improve overall health. As this thesis examines the mental health component of HRQL, operationalized by the domain of EWB, an important first step is the identification of a framework to guide research questions and interpret results.

There have been significant efforts to identify life experiences and circumstances that put mental health at risk. An approach taken by social scientists has been to postulate that differences in the risk of mental illness can be attributed to life experiences, exposure to stresses, and the social conditions in which one lives[1-13]. Simply put, these researchers approach the study of mental health from a perspective referred to as the stress process[1-3]. Described as a *process*, the focus of the research is to shift attention towards understanding the relationships among

factors causing or contributing to stress and understanding the ways these relationships develop, change, and contribute to mental health[1-3]. The interest is less about identifying factors associated with stress but rather in understanding how stress arises and how factors may be associated to each other. This process has not been widely used in research focused on children with epilepsy and EWB. However, given the successful application of the stress process in epidemiological and medical sociological studies of psychological distress and mental illness[1-13], the stress process could provide a unique lens to understand differences in EWB in children with epilepsy. Figure 3-1 describes the Stress Process Model used in this thesis.

3.1 The Stress Process Model of Emotional Well-Being in Childhood Epilepsy

The first domain in the stress process is the background and context of stress[1-4]. This describes the underlying characteristics of each person such as age, gender, ethnicity, economic status, and establishes social or economical differences among individuals that may influence the stress they are exposed to, their ability to attend to stresses, or how stress manifests itself[1-4]. Due to the underlying nature of the domain, it is less susceptible for targeted treatments compared to other components of the stress process.

The second domain of the stress process is stressors: those conditions or experiences that may lead to poorer mental health[1-4]. Stressors allow the opportunity to determine the importance of a particular stressor on a mental health outcome. Pearlin et al.[1-4] have argued that the origin of stress typically appears out of two circumstances, occurrence of discrete life events or the presence of chronic

problems, and these two sources can work synergistically to produce negative manifestations of stress. Stressors can be divided into primary and secondary, where primary stressors are those leading the stress process and secondary stressors are stressors that follow from it. This division allows the opportunity to explain how stressors follow sequentially in time and how a set of stressors can produce new stressors across time[1-4]. In this thesis, a diagnosis of epilepsy and living with epilepsy would be primary stressors and factors related to, or occurring because of epilepsy would be secondary stressors. Examples of factors related to epilepsy include the severity of epilepsy, frequency of seizures, number of antiepileptic drugs (AEDs), type of epilepsy, and severity of behavioural and cognitive problems, as each is hypothesized to occur sequentially in time, in response to the occurrence of epilepsy. In this thesis research, a parent experiencing depressive symptoms will be treated as a secondary stressor. While parental depressive symptoms may not occur in all cases due to the diagnosis of epilepsy itself, this stressor is believed to affect the process of EWB in a similar manner as other secondary stressors.

Mediators of stress comprise the third domain of the stress process and help to explain differences in the effects that the same stressor can have among individuals[1-4]. Mediators of stress act to produce variability in stress outcomes and are classified as either coping factors or social support factors[1-4]. Pearlin et al.[1-4] argues that understanding differences in coping responses and social support networks among individuals allows researchers are better able to understand the unequal manifestations of stress among individuals. In epilepsy research, stress

mediators represent social and coping resources available after the diagnosis of epilepsy that may act to reduce the impact of epilepsy on EWB.

In this thesis research, there was an opportunity to examine the role of three components of the family environment as being possible stress mediators or moderators. Rodenburg et al.[14] suggests categorizing components of the family environment based on a factor's proximity to the child's life, based on previous sociological findings[15-20]. Those factors that indicate the quality of the parent-child relationship are most proximal to the child's life and would qualify as mediators[14]. Factors representing the internal and external family characteristics and reflect the adaptability of the family would be deemed contextual family factors and act as moderators[14]. Within the stress process model, whether a factor is deemed a mediator versus a moderator is based upon the effects of the factor on the relationship between stressors and stress outcomes. Specifically, stress mediators intervene between onset of stress and the stress outcome to cause an indirect effect of the stressor that can be modified by altering the social or coping resources, while stress moderators alter the effect of the stressor based on the level of the resource. The stress process model describes these moderating resources as having "buffering" effects[21]. The description of a stress mediator or moderator leads decisions to classify a resource as a mediator or moderator based upon the resources effects in the stress process model rather than predetermined conceptual differences[3]. As such, a specific resource may have multiple roles based upon the effects it has on each stressor. In this thesis, family functioning, family demands, and family resources represent possible stress mediators or moderators.

Manifestations of stress and stress outcomes represent the final domain of the stress process[1-4], and are the health outcome of interest. In this thesis, that outcome is emotional well-being. As a whole, the stress process model in this thesis suggests that primary stressors (diagnosis of epilepsy and living with epilepsy) would manifest secondary stressors (epilepsy-related factors), acting directly or indirectly through stress mediators and moderators (family factors) to produce a stress outcome (level of EWB). The stress process model is the conceptual framework used to guide the process of identifying the pattern of inter-relations among epilepsy-related factors and family factors, to allow the opportunity to better target and modify risk factors in childhood epilepsy. The stress process model will not be empirically tested for its validity but rather was used to guide the analyses conducted to foster understanding of the inter-relationships. As such, not all relationships within the stress process will be examined and only the relationships between secondary stressors (epilepsy-related factors), possible stress mediators and moderators (family factors), and stress outcome (emotional well-being) will be examined. The goal of this thesis research is to better understand the role of both epilepsy-related and family factors on EWB as a step towards optimizing HRQL.

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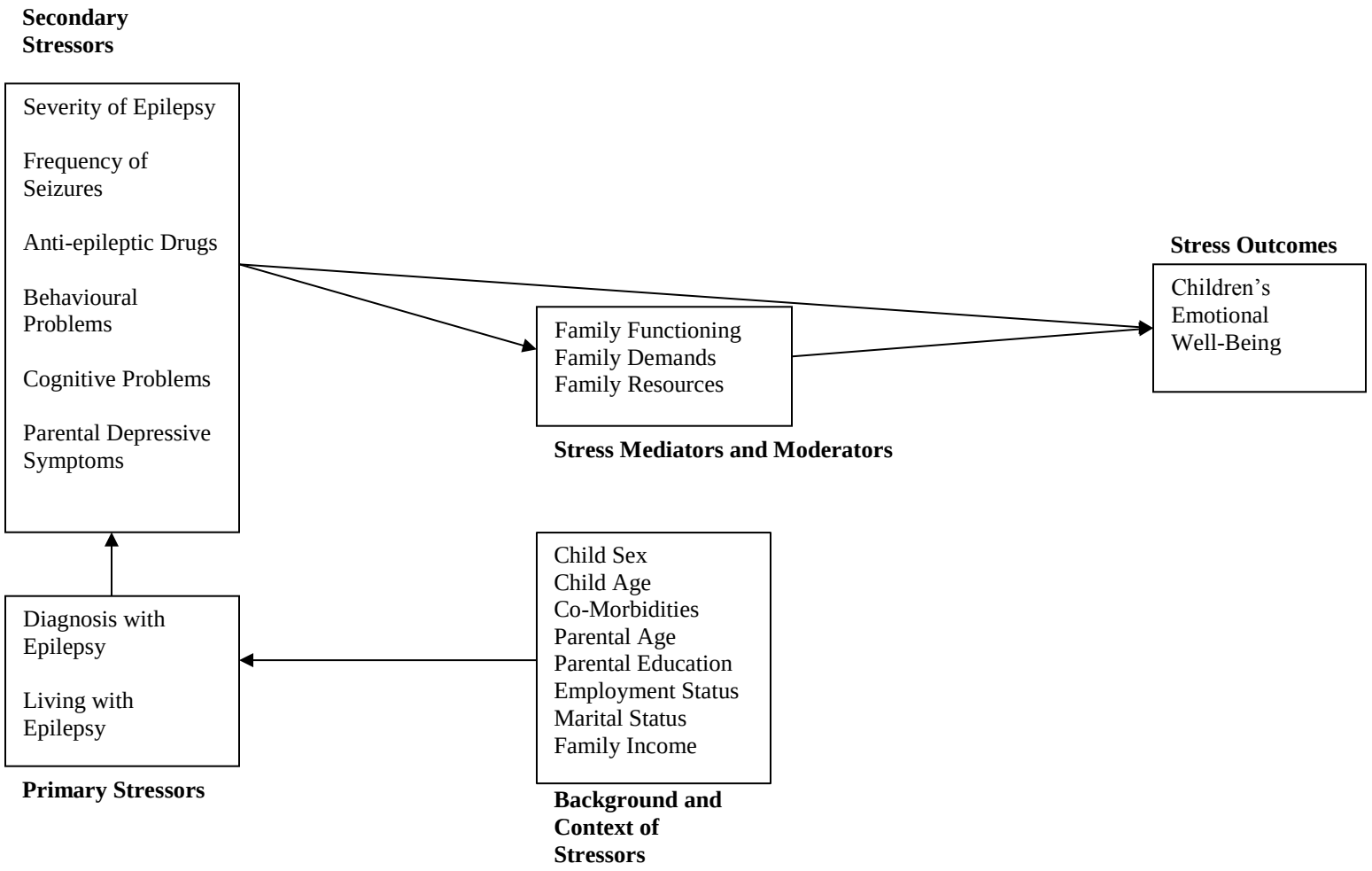
Figure 3-1. Conceptual framework used during thesis modified from the Stress Process Model.



Chapter 4: Development and Assessment of a Shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55)

4.1 Introduction

Epilepsy is one of the most common chronic neurological conditions in children, and is associated with increased risk for poor health-related quality of life (HRQL)[1-2]. These children experience difficulty in aspects of functioning, including emotional and behavioural problems, social competence, academic achievement, and family life, with effects extending into adulthood[3-7]. HRQL is regarded an important outcome in assessing the impact of chronic disease[8]. It refers to the "subjective and objective impact of dysfunction associated with an illness or injury, medical treatment, and health care policy.[9]" Currently, there are formal standards requiring claims of improvement in HRQL to provide evidence of significant change in all relevant dimensions (typically measured as the disease state and physical symptoms, functional status, psychological functioning, and social functioning)[9-11]. Including a comprehensive measure of HRQL is a challenge for clinicians and researchers due to variation among individuals, biases in interpretation of questions, and the considerable time burden related to the large number of questions associated with this multidimensional construct[12].

One epilepsy-related measure of HRQL is the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE). This measure was developed and validated in an Australian sample as a 73-item instrument[13] but was later revised for use in North American populations as a 76-item, 16 subscale instrument[14]. Despite wide-spread

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use, it has been suggested that the instrument may benefit from further revisions[15]. One shortcoming of the QOLCE is that a factor analysis was not performed during development[14]. Exploratory factor analysis provides an important role during construction and validation of measures by identifying non-necessary items and reducing the measure into a smaller number of factors. Factor analysis also provides insight into the underlying structure of the measure, allowing the opportunity to examine whether it aligns with previously conceptualized models. Furthermore, the usefulness of some subscales of the QOLCE containing a small number of items has been questioned. Such subscales include those measuring stigma (1 item), social activities (3 items), social interactions (3 items), energy/fatigue (2 items), and general quality of life (1 item). Low internal consistency reliability has been reported for some of the smaller subscales despite the acceptable reliability of the overall measure. To our knowledge, no studies have formally assessed the construct validity of the QOLCE, whether all items are necessary, or how well they align with the current conceptual understanding of HRQL. Valid and reliable measurement of HRQL that minimizes respondent burden is essential to provide clinicians, researchers, and patients with robust estimates of individual HRQL. Accordingly, the primary objective of this study was to develop and validate a shortened version of the QOLCE. A secondary objective was to compare baseline risk factors predicting HRQL 24 months post-diagnosis identified when using the shortened QOLCE and the original in the same sample.

4.2 Methods

4.2.1 Data source and participants

Data were obtained from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES), a multi-centre prospective cohort study that examined trajectories and determinants of HRQL in children ages 4 to 12 years with newly-diagnosed epilepsy during the first two years after diagnosis. Data were collected at four times: baseline (as close as possible to the time of diagnosis), 6, 12, and 24-months post-diagnosis. A two-stage clustered sampling strategy was employed. Every paediatric neurologist practicing in Canada was asked to participate by approaching parents of eligible children about the study. Paediatric neurologists identified 456 eligible patients whose parents were approached to participate. A total of 373 (82%) parents completed the baseline self-administered questionnaire, 336 completed 6-month questionnaire, 304 completed 12-month questionnaire, and 282 completed 24-month questionnaire. A more detailed description of the HERQULES methodology has been provided previously[16].

4.2.2 Measures

Health-related Quality of Life

The QOLCE[13] is an epilepsy-related, parent-report instrument designed to measure HRQL of children ages 4 to 18 years. It assesses seven dimensions of HRQL: cognition, physical activities, social activities, emotional well-being, behaviour, general health, and general quality of life. These seven dimensions are composed of 16 subscales, measured with a single or multiple items. Items are rated on a five-point Likert scale and then transformed to a score with a minimum of 0 (low

functioning) and a maximum of 100 (high functioning). The QOLCE total score is the unweighted mean of the subscale scores. In HERQULES, the internal consistency reliability as measured by Cronbach's alpha was 0.69-0.94 for each subscale and 0.92 for the overall measure.

The Child Health Questionnaire-Parent Form (CHQ)[17] 50-item version was also used. It is a generic, parent-report questionnaire measuring child health and well-being over the past four weeks. The CHQ incorporates 13 concepts measuring multiple aspects of child health and the impact of disease on the family. Two weighted and standardized summary scores are obtained measuring physical functioning and psychosocial functioning. The CHQ has been used successfully in a previous study of children with epilepsy[13]. In HERQULES, the internal consistency reliability, as measured by Cronbach's alpha, was 0.90 for the overall measure.

Family Environment

Parental depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D)[18], a 20-item self-report scale designed to measure depressive symptoms in the general adult population over the past four weeks. The CES-D uses a four-point Likert scale assessing the frequency of symptoms experienced. The total score ranges from 0 to 60, with higher scores indicating more depressive symptoms. In HERQULES, the internal consistency reliability, as measured by Cronbach's alpha, ranged from 0.75-0.80 across the four time points.

The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR)[19] scale was used to assess satisfaction with family relationships. It is a 5-

item instrument measured on a five-point Likert scale ranging from 0 (hardly ever) to 4 (almost always). Scores on individual items are summed to obtain a total score (0 to 20) indicating the level of satisfaction with family functioning (with higher scores representing greater satisfaction). In HERQULES, the internal consistency reliability, as measured by Cronbach's alpha, ranged from 0.86-0.89 across the four time points.

Family demands were assessed using the Family Inventory of Life Events and Changes (FILE)[20]. The 71-item FILE assesses family demands in terms of the number of life events experienced by each family member over the previous year. A total score is computed by summating of all "yes" responses, with higher scores representing more stress (0 to 71). In HERQULES, the internal consistency reliability, as measured by Cronbach's alpha, ranged from 0.83-0.98 across the four time points.

The Family Inventory of Resources for Management (FIRM) assesses resources families have available to aid their adaptation to stressful events[21]. The HERQULES study used two subscales, family mastery and health (20 items) and extended family social support (4 items). Items are rated on a four-point Likert scale and are summed to obtain a total score, with higher scores indicating more available resources. In HERQULES, the internal consistency reliability as measured by Cronbach's alpha ranged from 0.91-0.93 for the family mastery and health subscale and from 0.44-0.54 for the extended family support subscale, across the four time points.

Demographic characteristics of families, including parent's age, education, marital status, employment status, child sex, and household income were also collected.

Clinical Characteristics

Paediatric neurologists provided information on several of the children's clinical characteristics. They completed the Global Assessment of Severity of Epilepsy (GASE)[22], a single-item measure designed for neurologists to rate the severity of epilepsy on a seven-point scale ranging from 1 (extremely severe) to 7 (not severe at all). The GASE requires neurologists to make an assessment based on their clinical experience when answering the following question: "Taking into account all aspects of this patient's epilepsy, how would you rate its severity now?" Inter-rater reliability was found to be good; weighted kappa values for two independent raters were 0.90 (95% CI: 0.82, 0.98) and 0.95 (95% CI: 0.91, 0.98)[22].

Neurologists recorded types of epilepsy syndrome, which were coded in two ways using the ILAE Classification and Terminology[23-24]: broadly as generalized or partial, and by subtype [primary generalized, absence, simple/complex partial, secondary generalized, benign epilepsy of childhood with rolandic spikes (BECRS), BECRS and secondary generalized, or undetermined]. Medication use was measured as the number of antiepileptic drugs (AED) prescribed currently and total number ever. Neurologists also were asked to provide an educated assessment based on their clinical experience whether children had behavioural or cognitive problems and to indicate this on four-point and five-point Likert scales, with lower scores

representing milder problems. In this study physician-reported behavioural and cognitive problems were both dichotomized as present or absent.

4.2.3 Statistical Analysis

Both exploratory and confirmatory factor analyses were conducted using the baseline HERQULES data. Regression analyses were conducted using both baseline and 24-month data. For both factor analysis procedures, items of the QOLCE were used to obtain polychoric correlation matrices. Fabrigar et al.'s (1999)[25] recommendations to use exploratory factor analysis (EFA) to identify the measurement model and confirmatory factor analysis (CFA) to test the model were followed. Exploratory and confirmatory factor analysis, assessment of internal consistency reliability, and assessment of convergent and divergent validity used baseline data. Regression analyses used 24-month HRQL as an outcome and baseline data for all predictors and confounders.

Principal Component Analysis and Exploratory Factor Analysis

Using Mplus 7.1 (Muthén & Muthén), the original QOLCE items were used to obtain a polychoric correlation matrix that was then entered into an initial principal component analysis, with a varimax rotation and eigenvalues set to one, to estimate the likely number of factors. Cattell's scree plot and parallel analysis using 10,000 datasets at 95% confidence were used to determine the number of factors to retain. Once the number of factors to retain was decided, EFA was used to identify items to be considered for removal to improve the factor structure. Principal axis factor analysis was chosen as the common extraction method, and a promax (oblique)

rotation was used due to the moderate correlation between HRQL items across dimensions. Items were retained if they had factor loadings ≥0.32 on a single factor, with loadings on all other factors <0.32. After each analysis, the item with the lowest factor loading below 0.32 was identified and deleted. The analysis was rerun until all items met the above conditions

Confirmatory Factor Analysis

Based on the results of the EFA, a four-factor solution was tested using CFA on the baseline data. As the goal was to obtain a single overall score for the measure, keeping true to how the original QOLCE was envisioned, it was important to obtain a valid and reliable higher-order factor structure. As such, a higher-order solution was tested. The primary goal of testing CFA models is to determine the goodness of fit between the hypothesized model and the sample data. Weighted least squares means and variance adjusted (WLSMV) estimation was used to obtain all estimates. Using WLSMV in Mplus produces a polychoric correlation matrix for the analysis. Following recommendations by Bentler and Bonett (1980)[26], Browne and Cudeck (1992)[27], and Tabachnik and Fidell (2007)[28], the adequacy of model fit was evaluated using the following statistics to assess the degree of fit between estimated and observed variance: Bentler's Comparative Fit Index (CFI; where >0.90 is considered acceptable); Tucker-Lewis Index (TLI; where >0.90 is considered acceptable); root mean square of approximation (RMSEA; where <0.08 is considered acceptable and <0.06 is excellent); and the weighted root mean square residuals (WRMR; where <1.00 is considered good) [28-30]. Because the χ^2 test is

sensitive to sample size[28], it was examined but not used for decisions of model fit. The solution was rerun on 24-month data to examine whether results were stable.

Internal Consistency Reliability

Internal consistency reliability was calculated for the original QOLCE and the shortened QOLCE using Cronbach's alpha. Because the two versions of the measure do not have the same number of items, they are not directly comparable. As such, the Spearman-Brown Prophecy formula[31-32] was calculated to determine what the reliability of the shortened QOLCE would have been if it had 76 items while maintaining the current correlations of items between each.

Convergent and Divergent Validity

Convergent validity was examined by estimating the association between subscale scores and QOLCE total score to the relevant subscales of the Child Health Questionnaire using Spearman rho (ρ) (CHQ total score, physical functioning, and psychosocial functioning). A positive correlation of $\rho>0.32$, indicating ≥10% shared variance between the two scales, is considered to be evidence towards convergent validity[28]. Divergent validity was examined by estimating the association between dissimilar scales of the QOLCE and CHQ (QOLCE Physical with CHQ Mental, and vice versa). Weak correlations would suggest little to no relationship between the two scales providing evidence towards divergent validity[28].

Predictors of HRQL

Multiple regression was used to compare baseline predictors of HRQL at 24 months using the shortened QOLCE and the original QOLCE. Unadjusted associations between baseline risk factors and HRQL at 24 months were obtained with linear regression. Risk factors found to be significant were included in multiple regression models to obtain adjusted estimates. Using a backward, stepwise algorithm, baseline risk factors were identified as predictors of 24-month HRQL. The significance level for risk factors to enter and remain in the model was $\alpha=0.10$. Risk factors examined included child risk factors (child age, child sex, severity of epilepsy, neurologist-reported behaviour problems and cognitive problems, type of seizure, age of seizure onset, and number of AEDs), and family risk factors (parental depression, family functioning, family demands, family resources, parent age, parent sex, marital status, employment status, education attainment, and family income). Multiple regression models controlled for baseline HRQL. Comparisons between estimates for the two versions of the QOLCE were examined using the Method of Variance Estimates Recovery (MOVER)[33].

4.3 Results:

4.3.1 Sample Characteristics

At baseline, children in the sample had a mean age of 7.5 (SD 2.3) years and approximately half of the sample (52%) was male. In terms of epilepsy-related factors, 61% of children were experiencing partial seizures and 67% were prescribed AEDs. Neurologists reported behavioural problems in 15% and cognitive problems in 20% of children. The mean rating of 5.1 on the GASE reflected that this

sample of children had less severe epilepsy on average. Children had moderately high HRQL scores, with a mean QOLCE score of 71.0 (13.9). Parents had a mean age of 38.0 (6.1) years, 81% were married, and 67% were employed. Families tended to be socio-economically advantaged, with 56% of families having an annual salary of ≥$60,000 and 67% having completed post-secondary education. Additional baseline characteristics are presented in Table D-1.

4.3.2 Exploratory Factor Analysis

Principal component analysis combined with parallel analysis identified four factors to be retained. Exploratory factor analysis yielded a 58-item solution representing four dimensions of HRQL (18 items removed due to factor loadings <0.32). An additional 3 items were subsequently removed due to ambiguous loadings. General health, overall quality of life, and feeling different from others, all loaded onto both social functioning and emotional functioning dimensions equally, indicating high item ambiguity. Retaining these items would have made interpretation difficult and hindered the applicability of the measure. Furthermore, additional models that included these items on a single factor revealed worsened model fit (results not shown). As such a decision was made to drop these items. The rotated factor loadings of the retained 55 items are found in Table D-2. The number of items loading onto each dimension was as follows: Cognitive- 22 items; Emotional- 17 items, Physical- 9 items, Social- 7 items.

4.3.3 Higher-order Factor Structure

The higher-order factor structure of the shortened QOLCE was tested using CFA (see Figure D-1 for higher-order summary factor model). As shown in Figure D-1, each item loaded onto a single first-order factor and the four first-order factors were then loaded onto a single higher-order factor representing overall HRQL. In this way, each first-order factor represents a single dimension of HRQL. Table D-2 shows the standardized parameter estimates for the first-order items.

The model had acceptable fit to the baseline data: CFI= 0.944; TLI= 0.942; RMSEA= 0.058 (90% CI: 0.056-0.061); WRMR=1.582. First-order and higher-order factor loadings were strong, ranging from λ= 0.66-0.93 and λ= 0.66-0.85, respectively ($p<0.001$ for all, see Figure D-1). Model fit using the 24-month data was as follows: CFI= 0.952; TLI= 0.951; RMSEA= 0.059 (90% CI: 0.056, 0.062); WRMR=1.451, suggesting stability of results across time in this sample.

4.3.4 Internal Consistency Reliability and Convergent and Divergent Validity

Internal consistency reliability was found to be good for each subscale of the shortened measure and had improved compared to the original QOLCE. Estimates of Cronbach's alpha ranged from 0.82 to 0.97 for the individual subscales, and was 0.96 for the overall measure (Table D-3).

Convergent and divergent validity were examined by estimating the correlation of relevant subscales of the CHQ with the relevant subscale of the shortened QOLCE using Spearman ρ. For convergent validity correlations examined were moderate to strong: Total QOLCE score to Total CHQ score (ρ=0.38), QOLCE Emotional subscale to CHQ Psychosocial subscale (ρ=0.70), and QOLCE Physical

subscale to CHQ Physical Functioning subscale (ρ=0.42). For divergent validity correlations examined were weak: QOLCE Emotional subscale to CHQ Physical Functioning subscale (ρ=0.30), and QOLCE Physical subscale to CHQ Psychosocial subscale (ρ=0.31).

4.3.5 Predictors of HRQL

The secondary objective of the study was to compare baseline predictors of HRQL 24 months later to those observed in the same sample using the original QOLCE. Risk factors associated with 24-month HRQL were found to be the same using the shortened QOLCE and the original measure. Risk factors for HRQL in the unadjusted analysis were baseline HRQL, presence of cognitive problems, presence of behavioural problems, family functioning, family demands, family resources, number of prescribed AEDs, parental depressive symptoms, and family income (data not shown). These risk factors were included in the backward, stepwise multiple regression analysis, shown in Table D-4 for both the shortened QOLCE and the original measure. Using the shortened QOLCE, after controlling for baseline HRQL and number of AEDs, 24-month HRQL was associated with the absence of cognitive problems (β=26.95, p=0.001), higher family functioning (β=0.47, p=0.014), family demands (β=-0.33, p=0.008), and an interaction between baseline HRQL and cognitive problems (β=0.32, p=0.011). The model fit the data well with R^2=0.44, and $F_{6,260}$=34.57, p<0.001. Using the MOVER, no significant differences in effect estimates were found when comparing the shortened QOLCE to the original.

4.4 Discussion

To our knowledge, this is the first study to formally examine the factor structure of the QOLCE and the first to produce a shortened version of the QOLCE. Based on our results, we propose that this shortened 55-item QOLCE (i.e., QOLCE-55), offers a valid, reliable, and feasible measure of HRQL in children with epilepsy. Results from the current study provide evidence of the higher-order factor structure of the QOLCE-55 in assessing the domains of HRQL. We believe that the structure of the QOLCE-55 aligns well with conventional definitions of HRQL[34], suggesting HRQL is a multidimensional construct assessing functioning within four primary dimensions: physical, emotional, social, and cognitive. While cognitive functioning has typically been assessed as part of the functional status dimension of HRQL, we suggest that given the established connection between epilepsy and cognitive functioning[35-37], it is reasonable to consider cognitive functioning as one of the four major dimensions of HRQL in children with epilepsy.

Several structural changes are evident when comparing the QOLCE-55, derived via factor analysis, from its predecessors[13-14]. Four cognitive subscales ranging in size from as few as 3 to 8 items are reduced to a single "cognitive functioning" factor. Five subscales assessing behaviour and emotional well-being are reduced to a single "emotional functioning" factor. Three subscales assessing social function (one containing a single item and a second only two items) are now encompassed as part of a single "social functioning" factor with 7 items. Two subscales assessing physical function are reduced to a single "physical functioning" factor. Using the method of principal component analysis resulted in the greatest

reduction of items for the subscales assessing behaviour and emotional well-being, from the original 34 items down to 17. Items assessing social functioning were reduced by half (14 to 7) and the assessment of physical function was reduced by three items. Even though the number of subscales changed, all items assessing cognitive function from the original QOLCE were retained for inclusion in the QOLCE-55. Rather than impeding the assessment of HRQL by removing items, the current study shows that proper analysis of items for elimination results in a psychometrically more robust instrument with better internal consistency reliability among the subscales/factors.

This study also compared risk factors at diagnosis that predict HRQL 24 months later using the QOLCE-55 and the original version. Predictors of 24-month HRQL included an absence of cognitive problems, as reported by the neurologist, better family functioning, fewer family demands, and a qualitative interaction between baseline HRQL and cognitive problems, where 24-month HRQL was highest for children with high HRQL at baseline and the absence of cognitive problems whereas 24-month HRQL was lowest for children with high baseline HRQL and the presence of cognitive problems. The results found using the QOLCE-55 were similar to those found using the original measure, both in the magnitude and direction of effects. A more detailed discussion of these relationships has been published previously[16]. The invariance between findings has practical implications for investigators and health care professionals by providing assurance that results obtained previously will be comparable to future studies using the QOLCE-55.

The original QOLCE was shown to be sensitive to severity of epilepsy in a group of children with well-defined pharmacoresistent epilepsy with high seizure burden as well as being responsive to improved outcomes following epilepsy surgery[38,39]. We anticipate any discriminatory sensitivities of the original QOLCE will continue to hold true for the QOLCE-55.

We anticipate that the QOLCE-55 will reduce respondent burden relative to the original measure, which requires approximately 20 minutes to complete. We estimate that the time required to complete that QOLCE-55 will be approximately 12-14 minutes, given that nearly a third of items have been removed. Achieving high participation rates when using self-report questionnaires is challenging and research has shown that questionnaire length is a strong predictor of response rates when using self-reported measures[40]. It is important for researchers to minimize respondent burden while maximizing the quality of responses, and one method of doing so is reducing the length of the questionnaire. We believe that the QOLCE-55 provides a tool for clinicians and researchers that is psychometrically improved, captures the multidimensionality of HRQL, and can be completed efficiently.

This study has some limitations that need to be considered. While we have significantly reduced the original length of the QOLCE, it is still a fairly long measure compared to epilepsy-related HRQL measures. There is an assumption that disease-specific HRQL measures are more sensitive than generic measures and it is our hope that increased sensitivity is beneficial compared to using a shorter measure. Like the original, the QOLCE-55 is parent administered, without any input from the child, missing the opportunity to obtain information regarding the child's perception.

While it would be beneficial to obtain self-report data, the age of children in our sample made it difficult to obtain self-reports. Furthermore, the assessment of behavioural and cognitive problems was based on pediatric neurologists' subjective ratings rather than a formal diagnosis based on a standardized testing procedure. Although our sample size is relatively large compared to other studies and meets the recommended sample sizes for our specific analyses, factor analysis is particularly taxing on sample size due to the number of potential parameters to be estimated. Our sample is one of convenience and contains a relatively large proportion of children with mild epilepsy. It is unlikely, however, that including a wider spectrum of severity would have substantially changed the factor structure of the measure. In terms of the regression analysis, attrition may have affected the overall estimates of our predictors. There was a selective loss across the 24-month period resulting in a sample of higher functioning families. For this study, our goal was to attempt to reproduce the results obtained using the original QOLCE by using the shortened version, the QOLCE-55, on the same sample. Because the QOLCE-55 was validated on the same sample that was used to reduce the number of items, further research should attempt to replicate our results in different samples of children with epilepsy.

Several future research directions are recommended to extend the validation of the QOLCE-55. One logical step is to further describe the validity of the QOLCE-55 by examining measurement equivalence – between subgroups of children with epilepsy (e.g., boys vs. girls, younger vs. older children) and longitudinally. It would also be useful to further examine convergent validity and divergent validity by

correlating the QOLCE-55 with similar and dissimilar measures. Finally, examining predictive validity by investigating whether the QOLCE-55 can identify meaningful clinical events such as differences between severities of epilepsy would be useful. We are also currently examining the possibility of a shorter, 20-item measure in hopes to further reduce respondent burden.

In conclusion, these initial findings suggest that the newly proposed QOLCE-55 is a reliable and valid measure of HRQL and that the profile of risk factors identified using the QOLCE-55 is invariant compared to the original measure and would be a superior replacement. The QOLCE-55 is a refined version of the currently popular measure, with increased internal consistency, decreased number of items, and a sound factor structure. The QOLCE-55 may be a viable option to reduce respondent burden when assessing HRQL in children with epilepsy, if subsequent proposed assessments of validity produce consistent evidence.

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Table 4-1. Child and Parent Characteristics at Baseline.

	Baseline (n=373)
Child Factors	
Age, years	7.5 (2.3)
Male %	52
Seizure type, partial %	61
Prescribed AEDs %	67
Experiencing seizures %	93
Epilepsy severity, GASE	5 (1.2)
Cognitive problems %	20
Behaviour problems %	15
Health-related quality of life, QOLCE	71 (13.9)
Parent Factors	
Age, years	38 (6.1)
Female %	93
Married or living with a partner %	87
Employed %	67
Post-secondary education %	67
Annual household income ≥60,000 %	56

For continuous variables, values represent mean (standard deviation).

Table 4-2. Individual items and factor solution of the Exploratory and Confirmatory factor analysis.

	Rotated Factor oading	Standardized Factor Loading (standard error)	R^2 Estimates (standard rror)
Factor 1: Cognitive Functioning			
1. Had trouble understanding directions?	0.86	0.93 (0.01)	0.87 (0.02)
2. Had difficulty following complex instructions?	0.86	0.92 (0.01)	0.84 (0.02)
3. Had trouble understanding or following what others were saying?	0.83	0.89 (0.02)	0.78 (0.02)
4. Had difficulty following simple instructions?	0.81	0.91 (0.01)	0.83 (0.02)
5. Had trouble remembering things people told him/her?	0.80	0.84 (0.02)	0.70 (0.03)
6. Had trouble finding the correct words?	0.80	0.83 (0.02)	0.68 (0.03)
7. Found it hard remembering things?	0.79	0.84 (0.02)	0.66 (0.03)
8. Had trouble concentrating on a task?	0.79	0.86 (0.02)	0.74 (0.03)
9. Had trouble remembering things s/he read hours or days before?	0.79	0.81 (0.03)	0.65 (0.04)
10. Had difficulty doing one thing at a time?	0.78	0.85 (0.02)	0.72 (0.03)
11. Had difficulty reasoning or solving problems?	0.77	0.86 (0.02)	0.75 (0.03)
12. Had trouble understanding what s/he read?	0.77	0.82 (0.02)	0.68 (0.04)
13. Reacted slowly to things being said and done?	0.77	0.83 (0.02)	0.69 (0.03)
14. Had difficulty keeping track of conversations?	0.77	0.83 (0.02)	0.68 (0.03)
15. Had trouble remembering names of people?	0.75	0.71 (0.03)	0.51 (0.04)
16. Had trouble remembering where s/he put things?	0.73	0.73 (0.02)	0.53 (0.04)
17. Had difficulty concentrating on reading?	0.73	0.83 (0.03)	0.68 (0.03)
18. Planned to do something than forgot?	0.72	0.77 (0.03)	0.68 (0.03)
19. Had difficulty making plans or decisions?	0.71	0.82 (0.03)	0.68 (0.03)
20. Had trouble writing?	0.70	0.74 (0.03)	0.55 (0.04)

21. Had trouble talking?	0.67	0.72 (0.03)	0.52 (0.05)
22. Had difficulty attending to an activity	0.64	0.76 (0.02)	0.58 (0.03)
Factor 2: Emotional Functioning			
1. Felt no one cared?	0.73	0.63 (0.05)	0.40 (0.06)
2. Wished s/he was dead?	0.73	0.64 (0.07)	0.41 (0.09)
3. Felt nobody understood him/her?	0.67	0.80 (0.03)	0.64 (0.05)
4. Angered easily	0.62	0.67 (0.03)	0.45 (0.05)
5. Hit or attacked people	0.58	0.60 (0.04)	0.37 (0.05)
6. Felt happy?	0.56	0.60 (0.04)	0.36 (0.05)
7. Felt down or depressed?	0.56	0.69 (0.04)	0.47 (0.05)
8. Swore in public	0.55	0.56 (0.05)	0.31 (0.07)
9. Felt frustrated?	0.53	0.76 (0.03)	0.58 (0.05)
10. Demanded a lot of attention	0.53	0.64 (0.04)	0.41 (0.05)
11. Was socially inappropriate (said or did something out of place in a social situation)	0.53	0.81 (0.03)	0.66 (0.05)
12. Felt valued?	0.52	0.45 (0.05)	0.20 (0.04)
13. Worried a lot?	0.50	0.65 (0.04)	0.42 (0.05)
14. Was obedient	0.47	0.48 (0.05)	0.23 (0.05)
15. Felt pleased about achieving something?	0.46	0.45 (0.05)	0.20 (0.04)
16. Felt excited or interested in something?	0.45	0.55 (0.04)	0.31 (0.05)
17. Felt confident?	0.38	0.73 (0.04)	0.53 (0.05)
Factor 3: Social Functioning			
1. Limited his/her social activities (visiting friends, close relatives, or neighbours)?	0.81	0.79 (0.03)	0.62 (0.05)
2. Limited his/her leisure activities (hobbies or interests)?	0.79	0.73 (0.04)	0.53 (0.05)
3. How limited are your child's social activities compared with others his/her age?	0.77	0.80 (0.03)	0.65 (0.05)
4. Affected his/her social interactions at school or work?	0.76	0.90 (0.02)	0.81 (0.04)
5. Isolated him/her from others?	0.76	0.92 (0.03)	0.84 (0.05)
6. Made it difficult for him/her to keep friends	0.67	0.93 (0.04)	0.87 (0.07)
7. Frightened other people?	0.53	0.67 (0.05)	0.45 (0.05)

Factor 4: Physical Functioning			
1. Gone to parties without you or without supervision?	0.74	0.50 (0.06)	0.25 (0.06)
2. Stayed out over night (with friends or family)?	0.73	0.27 (0.07)	0.09 (0.06)
3. Played with friends away from you or your home?	0.72	0.59 (0.04)	0.35 (0.06)
4. Played freely in the house like other children his/her age?	0.67	0.84 (0.05)	0.71 (0.08)
5. Participated in sports activities (other than swimming)?	0.62	0.57 (0.05)	0.33 (0.06)
6. Been able to do the physical activities other children his/her age do?	0.58	0.87 (0.04)	0.75 (0.07)
7. Played freely outside the house like other children his/her age?	0.54	0.83 (0.04)	0.69 (0.06)
8. Gone swimming? (i.e. swam independently)	0.50	0.36 (0.04)	0.13 (0.05)
9. Needs more supervision than other children his/her age?	0.48	0.87 (0.04)	0.75 (0.06)

Parameter estimates were significant at $p < 0.001$

Table 4-3. Internal Consistency reliability of the original QOLCE and the Shortened QOLCE (Cronbach's alpha).

Domain	QOLCE, Range across (n) subscales*	QOLCE-55
Overall	0.92	0.96
Cognitive	0.85 to 0.94 (n=4)	0.97
Emotional	0.69 to 0.78 (n=4)	0.88
Social	0.85 and 0.85 (n=2)	0.89
Physical	0.77 and 0.80 (n=2)	0.82

*Three subscales of the original QOLCE only contain a single item and are unable to be used in the calculation of internal consistency. The original QOLCE contained a fifth dimension (Behaviour) and is excluded from above.

Table 4-4. Multiple regression analysis of baseline risk factors predicting Health-Related Quality of Life at 24-months.

Parameter	β (SE): Original QOLCE	β (SE): QOLCE-55	Δβ (95% CI)
Cognitive problems	37.56 (9.22)[a]	26.95 (8.17)[a]	-10.61 (-34.87, 13.65)
Family Functioning (APGAR)	0.45 (0.19)[c]	0.47 (0.19)[c]	0.02 (-0.50, 0.54)
Family Demands (FILE)	-0.33 (0.12)[b]	-0.33 (0.12)[b]	0.00 (-0.34, 0.61)
HRQL × Cognitive problems	0.49 (0.14)[c]	0.32 (0.13)[c]	-0.17 (-0.55, 0.21)

Adjusted for number of AEDs and baseline HRQL.
[a]p<0.001
[b]p<0.01
[c]p<0.05

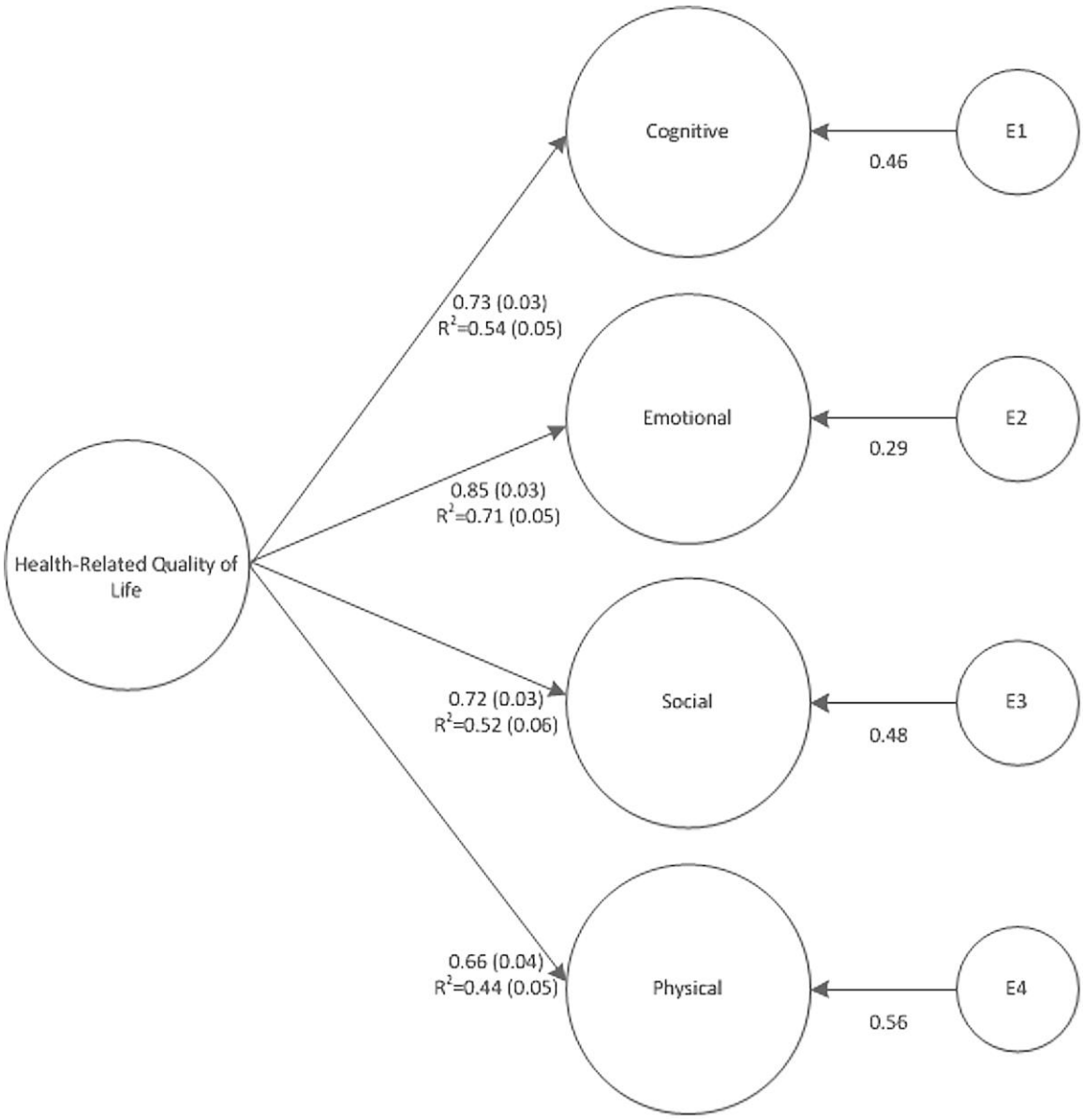

Figure 4-1. Higher-order summary factor model of the shortened QOLCE. All parameter estimates and R^2 values shown were standardized and significant at $p<0.001$. First-order items were not included for simplicity.

Chapter Five: Emotional Well-Being in Children with Epilepsy: Family Factors as Mediators and Moderators

5.1 Introduction

Childhood epilepsy is associated with an increased risk for poor health-related quality of life (HRQL)[1-3]. Psychosocial issues are more frequent in children with epilepsy including increased risks of emotional and behavioural problems, depression, anxiety, and poor self-esteem compared to healthy children [4-9]. One domain of HRQL, emotional well-being (EWB), is a balance between positive affects and negative affects[10]. EWB describes the psychological impact of a disease or disorder. Research on EWB presents the opportunity to identify modifiable risk factors associated with poor EWB and is a major step towards optimizing HRQL.

Multiple epilepsy-related factors have been found to be associated with poor EWB in children with epilepsy, including frequency of seizures[3,11,12], severity of epilepsy[13-14], or anti-epileptic drugs (AEDs)[12,15]. While little research has been conducted investigating the role of the family on EWB in children with epilepsy, research suggests poor family mastery[16], poor parental emotional support[16], low parental confidence[16], poor family adjustment and restrictive parenting[17], and negative child-parent or child-family interactions[17-20] are each associated with increased risks of behavioural and emotional problems. There is evidence suggesting that particular family factors may act as mediators between epilepsy-related factors and health outcomes. In one study, parents who believed their child

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would be stigmatized or who had rigid decision-making styles that placed restrictions on the child reported higher levels of behavioural problems in their child[21]. These authors also found that the effects of simple partial seizures were mediated by several factors related to parent-child interactions but that this was not true for other epilepsy-related factors[21]. Other factors have been suggested as possible mediation mechanisms for the effects of epilepsy-related factors on emotional or behavioural problems such as perception of the child as in poor health[22], a perception of the child as clumsy[22], poor perception of support[23], poor emotional adjustment[23], negative maternal attitude towards epilepsy[24], and high family stress[24]. In these cases, it is not always epilepsy itself that produces the effects but rather reactions to epilepsy. This finding stresses the importance of strengthening the family unit at diagnosis and post-diagnosis to limit or weaken the negative effects of epilepsy on the risk of behavioural and emotional problems, and overall HRQL.

The inclusion of family factors as mediating or moderating factors in the relationship between epilepsy-related factors and EWB may be supported in the Stress Process Model[25]. Briefly, the Stress Process Model is a conceptual framework used to understand relationships among a set of factors, called stressors, which are believed to contribute to a mental health outcome[25-28]. Under this framework, mental health outcomes are manifested as a result of both experiences and conditions within an individual's life[25-28]. Within the stress process there exists primary stressors (e.g. diagnosis or living with epilepsy) and secondary stressors (e.g. symptoms or epilepsy-related factors). Mediators and moderators play an

important role in the Stress Process Model to explain variable responses to the same stressor, and are typically coping or social support factors. Stress mediators intervene between the onset and stress outcome to cause indirect effects, while stress moderators alter the effect of the stress based upon an individual's levels of resources[29].

Our primary objective was to examine the relationships of epilepsy-related factors with a child's EWB two-years post-diagnosis, and examine if epilepsy-related factors are mediated or moderated by family factors. See Figure 5-1 for a graphical representation of the Stress Process Model used in this study. Our secondary objective was to assess the consequence of measuring EWB using only negative affect items as opposed to using both positive and negative affect items. When discussing mental health, we tend to turn towards psychopathologies such as depression or anxiety and measurement of EWB often ignores the positive aspects of mental health. We examine whether significant differences in estimates of EWB are obtained using the two measures and whether the set of predictors remains the same when using either configuration.

5.2 Methods:

5.2.1 Data source and participants

Data were obtained from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES), a multi-centre prospective cohort study of children ages 4 to 12 years. A two-stage clustered sampling strategy was used to recruit both paediatric neurologists and parents from across Canada. HERQULES identified 456 eligible parents and 373 (82%) completed baseline self-administered questionnaire.

Data were collected over two years post-diagnosis at four times: baseline (as close as possible to the time of diagnosis), 6, 12, and 24-months. Over the study, 336 parents completed the 6-month questionnaire, 304 completed the 12-month questionnaire, and 282 completed the 24-month questionnaire. A more detailed description of the HERQULES methodology has been previously reported[30,31].

5.2.2 Measures

Emotional Well-Being as a Health Outcome

The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)[31,32] was used to assess EWB in this study. The QOLCE is an epilepsy-specific, parent-report measure of HRQL for children ages 4 to 18 years. This study employed the 55-item version, QOLCE-55[31]. The QOLCE-55 assesses HRQL across four domains, with one assessing EWB. Each items is rated on a five-point Likert scale and then transformed to a score from 0 (low functioning) to 100 (high functioning). In HERQULES, the QOLCE-55 has demonstrated high internal consistency reliability, with a Cronbach's alpha of 0.96 overall and 0.88 for the EWB subscale at baseline.

Family Factors

Parental Depressive Symptoms: Parental depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D)[33], a 20-item self-report instrument measuring depressive symptoms using a four-point Likert scale. CES-D assesses the frequency of depressive symptoms over the past four weeks, resulting in a total score from 0 to 60, with higher scores representing more

depressive symptoms. In HERQULES, the internal consistency reliability was good, with Cronbach's alpha, ranging 0.75 to 0.80 across the four time points.

Family Functioning: Family functioning was measured with the Family Adaptability, Partnership, Growth, Affection, and Resolve (APGAR)[34]. APGAR has 5-items measured on a five-point Likert scale ranging from 0 (hardly ever) to 4 (almost always) and a total score (0 to 20) indicating the level of satisfaction with family functioning (where higher scores represent greater family satisfaction). In HERQULES, the internal consistency reliability of APGAR was high with Cronbach's alpha ranging from 0.86 to 0.89 across the four time points.

Family Demands: The Family Inventory of Life Events and Changes (FILE) was used to measure family demands[35]. FILE is a 71-item instrument assessing family stress, with a total score of 0 to 71, where higher scores indicate greater levels of stress on the family. In HERQULES, the internal consistency reliability of FILE was high with Cronbach's alpha ranging from 0.83 to 0.98 across the four time points.

Family Resources: Family resources were assessed using the Family Inventory of Resources for Management (FIRM)[36]. FIRM assesses resources families have available to aid their adaptation to stressful events. Family Mastery and Health (20 items) and Extended Family Social Support (4 items) were included in HERCULES, measured on a four-point Likert scale with higher scores indicate more resources. In HERQULES, the internal consistency reliability was high with Cronbach's alpha ranging from 0.91 to 0.93 for the Family Mastery and Health

subscale, and from 0.44 to 0.54 for the Extended Family Support subscale, across the four time points.

Epilepsy-related Factors

Information regarding epilepsy factors was collected through a neurologist report. Included in these reports was the Global Assessment of Severity of Epilepsy (GASE)[37], a single-item measure to rate the severity of epilepsy on a seven-point scale ranging from 1 (extremely severe) to 7 (not severe at all). Inter-rater reliability was high, with weighted kappa values for two independent raters of 0.90 (95% CI: 0.82, 0.98)[37].

Neurologists reported on other aspects of epilepsy including frequency of seizures, the number of anti-epileptic drugs (AEDs), and type of epilepsy syndrome. Type of epilepsy syndrome was coded in two ways using the ILAE Classification and Terminology[38,39]: broadly as generalized or partial, and by subtype. Neurologists reported on the severity of behavioural and cognitive problems using a four-point and five-point Likert scale, respectively. In this study, both presence of behavioural problems and cognitive problems were dichotomized.

Demographic Characteristics

Demographic characteristics of families, including parent's age, education, living with a spouse, employment status, and household income were also collected.

5.2.3 Statistical Analysis

Mplus 7.1 (Muthén & Muthén) was used for all analyses. Family factors were mean-centered for ease of interpretation. Epilepsy-related factors and family factors were analyzed from baseline while child EWB was measured at baseline and 24-months. EWB at 24-months was used as the outcome while EWB at baseline was used as an adjustment allowing the outcome to be conceptualized as the *change in emotional well-being* across the 24-months. Univariable linear regression assessed unadjusted associations between epilepsy-related and outcomes before multivariable analyses. Epilepsy-related factors that had a *P*-value of <0.20 during univariable modeling were included in each multivariable model.

Several models were examined to identify the effects of epilepsy-related factors and mediation and moderation effects of family factors. In model 1, the baseline model, only epilepsy-related factors, parental depressive symptoms, and confounders were included. Models 2, 3, and 4 each built off of this model by including a family factor for possible mediation effects. Model 2 included family functioning and Model 3 included family demands. Model 4 examined whether mediation occurred with both factors in the model simultaneously. Moderation effects were assessed using an interaction variable of family resources and each epilepsy-related factor. Only significant interaction variables are presented. Model 5 assessed the simultaneous mediating and moderating effects. The results of mediation and moderation of each individual epilepsy-related factor unadjusted by other epilepsy-related factors were also examined.

Mediation was examined both using the Baron and Kenny method[40] and the delta-method[41]. In the Baron and Kenny method the following criteria had to be met: the epilepsy-related factor need to be associated with the family factor; epilepsy-related factors need to be associated with child EWB; family factors need to be associated with child EWB[40]. To examine whether possible mediation effects were significant, the delta-method was used. This method uses the beta coefficients from the mediation model to obtain a mediation beta-estimate (*a*b*), and calculates the standard error of this estimate[41,42]. Coefficient *a* is obtained from the association between an epilepsy-related factor and a family factor, while coefficient *b* is obtained from the association between a family factor and EWB. Using maximum likelihood estimates *a, b* and their appropriate standard errors are obtained, and using a covariance term of zero between *a*b*, the delta method is simplified to the Sobel method and provides appropriate tests of significance[42].

To investigate the impact of using a negative-only measure of EWB, positive affect items were removed to create a negative-only item configuration. The previously described methods were then repeated using the negative-only item configuration, and results were examined for any differences to those previously obtained.

5.3 Results:

5.3.1 Sample Characteristics

At baseline, children had a mean age of 7.5 (SD 2.3) years and 52% was male. Children had relatively mild epilepsy, with a mean GASE of 5.1 on the GASE, and baseline EWB of 72.5 (SD 13.2). Mean age of parents was 38.0 (SD 6.1) years, 87%

were living with a spouse, 67% were employed, and 67% had completed post-secondary education. Mothers reported the vast majority of responses. Additional baseline characteristics are reported in Table 5-1 and 5-2.

5.3.2 Univariable Results

Univariable analyses resulted in the following being included in the multivariable model: GASE, frequency of seizures, AEDs, presence of behavioural problems (no, yes), presence of cognitive problems (no, yes), and parental depressive symptoms.

5.3.3 Mediation Effects of Family Functioning and Family Demands

Parental depressive symptoms were the only factor to be mediated by family functioning and family demands (Tables 5-3 and 5-4) while the presence of behavioural problems was mediated by family functioning when tested individually (Table 5-5). Family functioning reduced the magnitude of the direct effect of parental depressive symptoms on EWB by 75% (-0.12 vs. -0.03), while family demands reduced this magnitude by 33% (-0.08 vs. -0.12). The inclusion of both family factors simultaneously reduced the magnitude of the direct effect by 92% (0.01 vs. -0.12). Family resources were found to partially mediate both family functioning and family resources in a multiple mediation pathway ($p<0.002$ for both, see Tables 5-6).

5.3.4 Moderating Effects of Family Resources

An interaction between family resources and severity of epilepsy was found (see Table 5-3). As the severity of epilepsy decreased (indicated by an increase in the GASE), the magnitude of the benefit received by family resources decreased.

5.3.5 Consequences of Using a Negative-Only Item Configuration

EWB at 24-months was lower using the full measure compared to the negative-only item configuration, but this was not statistically significant (74.8 vs. 76.4, p=0.11). The same set of predictors was found using the negative-only item configuration compared to the full measure and was similar in both magnitude and direction. An interaction between behavioural problems and family resources was found using the negative-only measure that was not previously obtained using the full measure.

5.4 Discussion:

The goal of this study was to elucidate the relationship between epilepsy-related factors and the family environment, specifically family functioning, family demands, and family resources. Our results indicated that family functioning and family demands were the strongest predictors of EWB 24-months post diagnosis. Parental depressive symptoms have been found to be associated with poorer HRQL in children with epilepsy[30,43], and our study suggests that this relationship is mediated indirectly through family factors. This is consistent with another study that classified aspects of the family environment to examine their relationship with epilepsy-related factors and depressive symptoms[44]. These authors found that

proximal family factors mediate the effects of parental depression on children's externalizing problems and delinquent behavior[44], similar to our findings regarding the relationship of parental depressive symptoms and, family factors with children's EWB.

Beyond parental depressive symptoms, we found that family factors did not mediate the relationships of any epilepsy-related factors with EWB. Unexpectedly, we did find evidence to suggest that both family functioning and family demands were partially mediated by family resources. Family resources in our study refer to the internal resources available to families to adapt to stressful situations, and these resources are important in determining the ability to cope. It is reasonable to suggest that near diagnosis, those factors have a large role in the child's ability to cope. In this case, resources are acting both as a mediator and moderator and would explain the results obtained. While this finding has not been examined previously in childhood epilepsy, it is consistent with a study of caregiver health, where increases in primary stressors (physical symptoms) did not directly increase changes in mental health outcomes, but rather it was those psychosocial resources that were found to be related to changes in stress outcomes across time[45].

We did find a significant interaction between the severity of epilepsy and family resources. In this case, children who have milder epilepsy receive less benefit to their EWB from increases in family resources. Furthermore, those with more severe epilepsy receive more benefits from increases in family resources, particularly if family resources were initially low at baseline. This finding provides

an opportunity to better prioritize allocation of resources in interventions at diagnosis for improving EWB.

A secondary objective of this study was to elucidate the role of positive affect items in the measurement of EWB in children with newly diagnosed epilepsy. We did not find any significant differences in both estimates and the set of risk factors using a negative-only item configuration. We did find a previously non-significant interaction to be statistically significant when using the negative-only measure. It is unknown whether this interaction is simply an artifact of removing the positive items. It is possible that this interaction holds true for only a subsection of the sample that becomes strengthened by the removal of positive items. Both the presence of behavioural problems and family resources are strongly associated with EWB.

A major strength of our study was the ability to include multiple aspects of the family environment in addition to clinical data regarding epilepsy in a longitudinal study. By capturing multiple factors relevant to the family environment, more complex relationships among factors could be examined, providing opportunities to identify specific areas of intervention in the effort to maximize a child's EWB and overall HRQL.

One limitation of this study is the reliance on parent-report, without the child self-report on both their EWB and on their perception of their family environment. Due to the age of our sample and the geographic spread of families, self-report from the child was not feasible. A possible issue of parental report is the potential for parental depressive symptoms to influence the reporting of their child's HRQL and

in turn EWB. Despite the relatively large proportion of parents with depressive symptoms, we do not believe this was likely to have influenced the reporting of EWB. A previously reported analysis using the HERQULES dataset found that maternal depressive symptoms had a small influence on parents' reporting on items related to energy or fatigue but did not influence reporting on other areas of HRQL[46]. In our study we used the QOLCE-55 version that does not contain items on energy or fatigue and as such the influence of parental depressive symptoms should not be an issue. A final possible issue is that our sample contains a relatively large proportion of children with mild epilepsy that may limit opportunities to observe some effects of epilepsy factors on EWB.

Future research could build upon the findings of this study by examining additional components of the family environment and assessing groups of children with more severe epilepsy. Further elucidating the mechanisms through which family factors and epilepsy-related factors affect and EWB would be beneficial in understanding the role of the family.

To our knowledge, this study is the first to comprehensively examine the relationship among epilepsy-related factors and the family environment on childhood EWB. The family environment appears to be an important component in the treatment of childhood epilepsy suggesting both clinicians and researchers should include measures of the family environment during treatment strategies. Interventions aimed at strengthening the family environment through improving the quality of the parent-child relationship or by improving family adaptability to

stress may help improve the long-term EWB and HRQL of a child with newly-diagnosed epilepsy.

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Table 5-1. Parent Characteristics at Baseline.

	Baseline (n=373)	6 month (n=336)	12 month (n=304)	24 month (n=282)
Marital Status				
Living with a Spouse	87	87	88	88
Other	13	13	12	12
Annual Household Income				
Less than $20,000	8.0	9.5	5.3	3.9
$20,000-$39,999	14.3	13.3	14.5	11.5
$40,000-$59,999	21.4	20.0	18.1	19.2
$60,000-$79,999	19.4	17.5	18.1	20.4
$80,000 or more	37.0	39.7	44.0	45.0
Age- Primary caregiver mean (SD)	37.7 (6.1)	38.2 (5.8)	39.1 (5.9)	40.3 (5.6)
Education – Primary caregiver				
Less than 8 years	1.9	0.6	0.3	0.4
8-12 years	9.4	8.0	6.3	5.3
High school	22.2	21.1	19.7	19.5
Vocational/Technical training	13.1	10.7	13.8	11.4
College/University	44.7	48.8	51.0	51.8
Graduate school	8.8	8.3	8.6	11.7
Employment status – Primary caregiver				
Employed	67.1	70.7	73.5	77.0
Not Employed	32.9	29.3	26.5	23.0
Parental Depression	37.2	25.9	24.9	21.4
Resources, FIRM mean (SD)	50.1 (11.1)	51.0 (11.2)	51.0(11.5)	50.7 (11.5)
Demands, FILE mean (SD)	9.5 (6.5)	N/A	8.0 (6.0)	7.9 (5.7)
Functioning, APGAR mean (SD)	13.9 (3.8)	14.1 (3.7)	13.9 (4.0)	14.1 (3.9)

Reported as percentages, unless otherwise stated

Table 5-2. Child Characteristics at Baseline.

		Baseline (n=373)	6 month (n=336)	12 month (n=304)	24 month (n=282)
Age, years	mean (SD)	7.5 (2.3)	7.9 (2.4)	8.5 (2.3)	9.5 (2.3)
Sex	Male	52.4	51.5	50.7	51.6
Epilepsy severity					
Extremely severe		0.3	0.3	0.0	0.3
Very severe		1.1	0.0	0.6	1.0
Quite severe		4.7	3.0	1.5	1.0
Moderately severe		17.0	8.3	6.7	6.0
Somewhat severe		23.6	14.8	12.7	7.6
A little severe		36.0	30.6	32.0	26.6
Not at all severe		17.3	43.0	46.5	57.8
Seizure type					
Partial		59.6	39.2	58.4	57.8
Generalized		38.5	59.0	39.8	39.5
Undetermined		1.9	1.7	1.8	2.7
Frequency of Seizures	mean (SD)	3.3 (1.7)	1.9 (1.3)	1.7 (1.1)	1.6 (1.0)
Current AED use		67.1	81.0	81.8	76.5
Total AEDs Taken	mean (SD)	0.8 (0.7)	1.2 (0.9)	1.3 (1.1)	1.4 (1.3)
Cognitive Problems		20.0	23.0	25.5	28.4
Behaviour Problems		15.4	23.6	20.7	22.7
QOLCE	mean (SD)				
Emotional Well-Being		72.5 (13.2)	73.8 (12.8)	74.4(13.0)	75.1 (12.9)

Reported as percentages, unless otherwise stated

Table 5-3. Unstandardized multivariable linear regression results assessing mediation and moderation.

	Model 1	Model 2	Model 3	Model 4	Model 5
Intercept	52.09 (8.06)	57.88 (7.85)	54.34 (8.01)	59.61 (7.81)	61.30 (7.61)
AED Use	-0.17 (1.17)	-0.46 (1.13)	-0.46 (1.17)	-0.70 (1.12)	-0.72 (1.08)
Frequency of Seizures	-0.15 (0.41)	-0.37 (0.39)	-0.16 (0.40)	-0.37 (0.39)	-0.43 (0.38)
Severity of Epilepsy (GASE)	0.11 (0.58)	-0.13 (0.56)	0.05 (0.57)	-0.17 (0.55)	-0.10 (0.53)
Behaviour Problems	-6.25 (2.07)[a]	-5.56 (1.99)[a]	-6.10 (2.04)[a]	-5.46 (1.97)[a]	-5.34 (1.95)[a]
Cognitive Problems	-3.51 (1.99)[b]	-3.56 (1.92)[b]	-3.55 (1.97)[b]	-3.60 (1.90)[b]	-2.17 (1.85)
Depressive Symptoms (CES-D)	-0.12 (0.07)[b]	-0.03 (0.07)	-0.08 (0.07)	0.01 (0.07)	0.05 (0.07)
Family Functioning (APGAR)	*	0.85 (0.19)[a]	*	0.82 (0.19)[a]	0.72 (0.20)[a]
Family Demands (FILE)	*	*	-0.29 (0.12)[a]	-0.25 (0.12)[a]	-0.13 (0.12)
Family Resources (FIRM)	*	*	*	*	1.03 (0.26)[a]
GASE*FIRM Interaction	*	*	*	*	-0.16 (0.05)[a]

All models adjusted for baseline emotional well-being, living with a spouse, parental education, and household income.
[a]$p<0.05$, [b]$p<0.1$

Table 5-4. Unstandardized mediating effects on the relationship between parental depressive symptoms and emotional well-being.

	Equation 1	Equation 2	*ab*	*Z*-value	*P*-value
Mediator: Family Functioning (Model 2)					
Intercept	57.88 (7.85)	-0.01 (0.19)	-0.12 (0.03)	-3.84	0.001
Depressive Symptoms	-0.03 (0.07)	-0.14 (0.02)			
Family Functioning (APGAR)	0.85 (0.19)				
Mediator: Family Demands (Model 3)					
Intercept	54.36 (8.02)	0.22 (0.33)	-0.07 (0.03)	-2.30	0.02
Depressive Symptoms (CES-D)	-0.08 (0.07)	0.23 (0.03)			
Family Demands (FILE)	-0.29 (0.12)				

Values denote β-coefficients (standard error)
Equation 1 is obtained from the regression of parental depressive symptoms, family functioning/demands, and emotional well-being.
Equation 2 is obtained from the regression of parental depressive symptoms on family functioning/demands.
ab is the coefficient obtained when multiplying the family functioning/demands coefficient from equation 1 by the depressive symptoms coefficient in equation 2.

Table 5-5. Unstandardized multivariable linear regression results assessing mediation and moderation using individual epilepsy-related factors.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Intercept	42.96 (5.85)	41.92 (5.87)	38.51 (6.13)	51.10 (6.38)	50.99 (6.40)	38.20 (5.62)
AED Use	-0.35 (1.15)	*	*	*	*	*
Frequency of Seizures	*	-0.49 (0.38)	*	*	*	*
Severity of Epilepsy (GASE)	*	*	0.15 (0.53)	*	*	*
Behaviour Problems	*	*	*	-6.03 (1.92)[a]	*	*
Cognitive Problems	*	*	*	*	-5.52 (1.81)[a]	*
Depressive Symptoms (CES-D)	*	*	*	*	*	0.01 (0.07)
Family Functioning (APGAR)	0.88 (0.19)[a]	0.91 (0.19)[a]	0.82 (0.19)[a]	0.83 (0.18)[a]	0.85 (0.18)[a]	0.85 (0.19)[a]
Family Demands (FILE)	-0.23 (0.12)[a]	-0.24 (0.11)[a]	-022 (0.11)[b]	-0.18 (0.11)	-0.19 (0.11)[b]	-0.24 (0.12)[a]
Significant Mediation	No	No	No	Yes; APGAR	No	Yes; Both

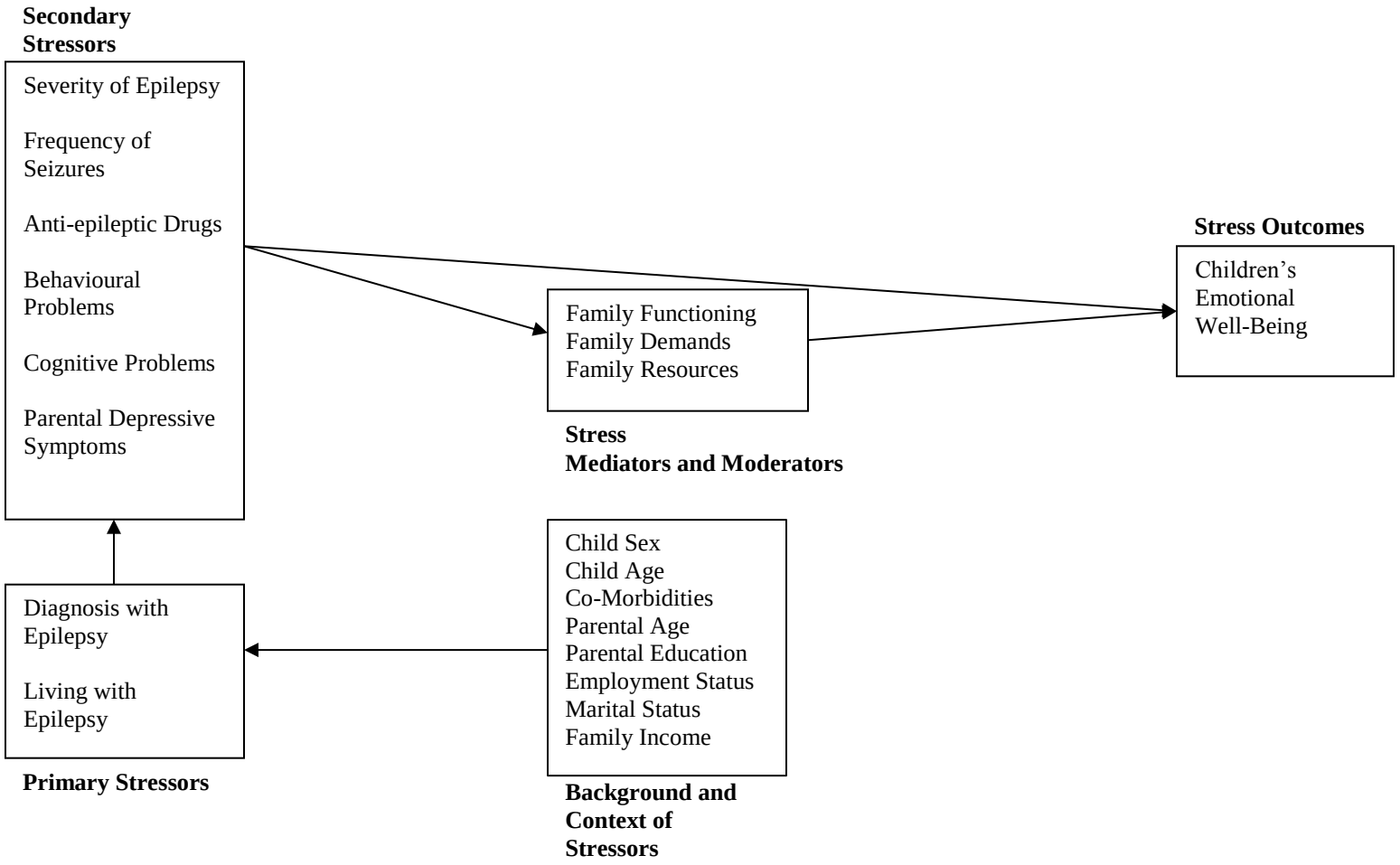
All models adjusted for baseline emotional well-being, living with a spouse, parental education, and household income.
[a]$p<0.05$, [b]$p<0.1$

Table 5-6. Unstandardized multiple mediating effects on the relationship between parental depressive symptoms, family functioning or family demands, family resources, and emotional well-being.

	Equation 1	Equation 2	*ab*	*Z*-value	*P*-value
Mediator: Family Resources (Model 5)					
Intercept	61.33 (7.61)	0.06 (0.46)	-0.12 (0.04)	-3.08	0.002
Depressive Symptoms (CES-D)	0.06 (0.07)	-0.30 (0.05)			
Family Demands (FILE)	-0.13 (0.12)	-0.53 (0.08)			
Family Resources (FIRM)	1.02 (0.26)				
Intercept	61.33 (7.61)	0.18 (0.33)	-0.03 (0.03)	-1.14	0.256
Depressive Symptoms (CES-D)	0.06 (0.07)	0.22 (0.03)			
Family Demands (FILE)	-0.13 (0.12)				
Intercept	61.33 (7.61)	0.06 (0.46)	-0.14 (0.04)	-3.17	0.002
Depressive Symptoms (CES-D)	0.06 (0.07)	-0.30 (0.05)			
Family Functioning (APGAR)	0.72 (0.20)	1.02 (0.14)			
Family Resources (FIRM)	1.02 (0.26)				
Intercept	61.33 (7.61)	0.03 (0.19)	-0.10 (0.03)	-3.27	0.001
Depressive Symptoms (CES-D)	0.06 (0.07)	-0.13 (0.02)			
Family Functioning (APGAR)	0.72 (0.20)				

Values denote β-coefficients (standard error)

Figure 5-1. Conceptual Framework used based on the Stress Process Model.



Chapter Six: Trajectories of Emotional Well-Being in Children with Newly Diagnosed Epilepsy

6.1 Introduction

Health-related quality of life (HRQL) has been well established as an important health outcome. While physicians and patients may differ in their priorities regarding health, improving HRQL is a shared major goal in treatment strategies. This priority has resulted in the pursuit of longitudinal data and the possibility to track changes in patients' HRQL. Despite this, little is known regarding the course of HRQL for many patient populations, and this is especially true for children with epilepsy. Less is known regarding emotional well-being (EWB), one domain of HRQL representing the psychological impact of the disease, and the changes that occur after a diagnosis of epilepsy. Epilepsy in childhood places a significant burden on both the child and family through physical symptoms, psychosocial problems, and may result in compromised HRQL for the child[1-7].

It is important to develop a better understanding of how a child adapts to a diagnosis of epilepsy and how this process differs among children. Examination of trajectories permits the opportunity to investigate both individual and group-average trajectories as a vehicle to understand health as a dynamic *process*. The use of trajectories to examine change is common in sociology, psychology, and some areas of public health[8-13] but less so in childhood epilepsy. Individual and group-average trajectories may resolve inconsistencies found in research by taking into account heterogeneity within the sample[14].

A version of this section is being prepared to be published elsewhere as Goodwin SW, Wilk P, Campbell MK, Speechley KN. Trajectories of Emotional Well-Being in Children with Newly Diagnosed Epilepsy.

In this paper, we investigate trajectories of EWB over the first two years post diagnosis in children with epilepsy. First, we identify the group-average trajectory of EWB and estimate variability in the parameters that define the trajectory. Second, we attempt to account for any across-children variability in the trajectory by using epilepsy-related factors and family factors. Third, we investigate whether multiple trajectories exist that would explain individual differences and account for unexplained variability, and assess which factors are associated with group membership to a particular trajectory group.

6.2 Methods

6.2.1 Data source and participants

Participants for this project were part of the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES). HERQULES is a multi-centre prospective cohort study examining trajectories and determinants of HRQL in children with newly diagnosed epilepsy. Children were between the ages of 4 to 12 years and had been newly diagnosed with epilepsy. Paediatric neurologists (53 of 72) identified 456 eligible patients and parents; 373 (82%) completed the baseline self-administered questionnaire. Four collection points were administered: baseline (as close as possible to the time of diagnosis), and approximately 6, 12, and 24-months after diagnosis. A total of 336 parents completed the 6-month questionnaire, 304 completed the 12-month questionnaire, and 282 completed the 24-month questionnaire. A more detailed description of the HERQULES methodology has been previously reported[15].

6.2.2 Measures

Emotional Well-Being as a Health Outcome

EWB was measured using The Quality of Life in Childhood Epilepsy Questionnaire-55 (QOLCE-55)[16,17], a 55-item epilepsy-specific measure of HRQL containing an EWB subscale. Each subscale is measured on a five-point Likert scale and scores from 0 (low functioning) to 100 (high functioning). In HERQULES, the QOLCE-55 had good internal consistency reliability, (Cronbach's alpha: 0.96 overall and 0.88 for the EWB).

Family Factors

Parental Depressive Symptoms: Center for Epidemiological Studies Depression Scale (CES-D)[18], a 20-item self-report, was used to assess parental depressive symptoms. Using a four-point Likert scale, CES-D assesses the frequency of depressive symptoms, resulting in a score from 0 to 60, with higher scores representing more depressive symptoms. Internal consistency reliability in HERQULES was good (Cronbach's alpha, ranged from 0.75 to 0.80).

Family Functioning: Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR)[19] assessed family functioning using 5-items measured on a five-point Likert scale. Item are summed to obtain a total out of 20, where higher scores represent greater family satisfaction. Internal consistency reliability in HERQULES was good (Cronbach's alpha 0.86 to 0.89).

Family Demands: Family Inventory of Life Events and Changes (FILE)[20] assessed family demands. FILE contains 71 items assessing family stress by totaling the number of stressful life events, with higher scores representing more stress.

Internal consistency reliability in HERQULES was good (Cronbach's alpha 0.83 to 0.98).

Family Resources: Family Inventory of Resources for Management (FIRM)[21] assessed level of family resources. FIRM assesses resources available to aid adaptation to stress across different fields, with Family Mastery and Health (20 items) and Extended Family Social Support (4 items) included in HERQULES. Items are measured on a four-point Likert scale and higher scores indicate more resources. Internal consistency reliability in HERQULES was good for Family Mastery and Health but inadequate for Extended Family Support (Cronbach's alpha 0.91 to 0.93 and 0.44 to 0.54).

Epilepsy-related Factors

Global Assessment of Severity of Epilepsy (GASE)[22] assessed severity of epilepsy using a single-item on a seven-point scale ranging from 1 (extremely severe) to 7 (not severe at all). Inter-rater reliability was good, with weighted kappa values for two independent raters of 0.90 (95% CI: 0.82, 0.98)[22]. Neurologists provided information on number of anti-epileptic drugs (AEDs), and type of epilepsy syndrome. Type of epilepsy syndrome was coded using the ILAE Classification and Terminology[23,24]: broadly as generalized or partial, and by subtype. Neurologists indicated severity of behavioural and cognitive problems using four-point and five-point Likert scales. Both dichotomized such that 0 represents no problems and 1 represents the presence of a problem.

Demographic Characteristics

Demographic characteristics included in this study were parent's age, education, whether they are living with a spouse or partner, employment status, and household income.

6.2.3 Statistical Analysis

Mplus 7.1 (Muthén & Muthén) was used for all analyses. All family factors, including CES-D scores, were mean-centered for ease of interpretation. Epilepsy-related factors and family factors were analyzed using baseline data while children's EWB was included at four time-points: baseline, 6, 12, and 24-months post diagnosis. Analyses were conducted over several steps, each contingent on the previous step. Maximum Likelihood (ML) estimation was used to obtain all parameters. Due to non-normal data (see Appendix E), all analyses were also run using Maximum Likelihood with robust standard errors (MLR). The results of ML and MLR did not significantly differ.

Unconditional latent growth curve modeling was used to construct a group-average trajectory of EWB across the four times. The group-average trajectory is a function of the mean intercept, a trend coefficient, mean slope, and random error[25]. In this study, the trend coefficient was fixed to 0, 1, 2, 4. A schematic diagram of this growth model can be found in Figure 6-1. We examined the possibility of linear growth, intercept-only growth or quadratic growth as the shape of the trajectory by comparing Bayesian Information Criteria (BIC), Chi-Square Test, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Standardized Root Mean Residual (SRMR).

If significant residual variance was identified, we then moved to a conditional growth model by including predictors to help explain any significant variation. Predictors included were severity of epilepsy (GASE), AEDs, presence of behavioural or cognitive problems, level of parental depressive symptoms (CES-D), family functioning (APGAR), family demands (FILE), and family resources (FIRM).

If significant variation around the group-average trajectory existed after inclusion of predictors, growth mixture modeling was used to cluster groups of similar individuals into the same class and obtain class-specific trajectories with greater homogeneity within a trajectory. While Growth Mixture Modeling can be used in a two-stage process[9], in our research we used a single step approach, where variables are added during the establishment of the trajectories to use information from the variables to better establish membership to each class[10]. Research suggests that if variables have direct effects on the trajectory, then including them during establishment of the trajectory is necessary to maximize likelihood of obtaining correct membership within a class[10]. The costs of doing so are increased complexity during model building and a potential loss of parsimony[9-11, 26-28].

To determine the best fitting model, a combination of indicators of fit were used: the bootstrap likelihood ratio test (BLRT) and Lo-Mendell-Rubin Likelihood Ration Test (LMR-LRT), BIC and adjusted BIC (aBIC), theoretical justifications, successful convergence, high entropy (near 1.0), greater than 1% of sample within a class, and high posterior probabilities while having low off-diagonal probabilities[9,26].

Comparisons among different class trajectories were conducted using t-tests (for 2-class models) or Analysis of Variance (>2 class models) at each time-point.

Logistic regression within growth mixture modeling was used to examine which variables predict membership to a particular trajectory class.

6.3 Results

6.3.1 Sample Characteristics

At baseline, children had a mean age of 7.5 (SD 2.3) years, and 67% were on at least one AED. Behavioural problems were present in 15% of children and cognitive problems in 20% of children. Children had mild epilepsy with a mean of 5.1 on the GASE. More baseline characteristics are found in Table 6-1.

6.3.2 Unconditional Latent Growth Model

Intercept-Only, Linear, and Quadratic unconditional latent growth models were tested as possible trajectory shapes. Model fit was good and approximately equal for linear and quadratic models (BIC: 9382 vs. 9400; RMSEA: 0.03 vs. 0.001; CFI: 1.00 for both; SRMR: 0.04 vs. 0.005, respectively). In the Quadratic model, the mean and variance for the quadratic slope were not significant (p=0.10 and p=0.35 respectively) and therefore, following guidance from Muthén LK (2010)[29], was rejected. The quadratic model was also not significantly improved compared to the linear model (-2LL X^2= 3.1, df=1, p> 0.05).

Children had a mean EWB score of 73.0 at baseline and this on average increased by 0.5 points every six months. Variance of intercepts and slopes was 121.3 (p<0.001) and 4.3 (p<0.001), respectively, indicating heterogeneity for both intercept and slope. Residual variances were significant at all time points,

suggesting unexplained variation still exists. See Table 6-2 for more details and Figure 6-2 for plots of individual and group-average trajectories.

6.3.3 Conditional Latent Growth Model

The set of epilepsy-related and family factors reduced the variance for the intercept by 35%, from 121.3 to 78.6. The variance in slope was less affected by inclusion of predictors, decreasing 12% from 4.3 to 3.8. Children with no behavioural or cognitive problems, fewer family demands, more family resources, and a higher functioning family had a higher baseline EWB ($p<0.05$ for each). Level of family resources and an interaction between the severity of epilepsy and family resources were found to be associated with the trajectory slope ($p=0.001$ for both), indicating that the increase in EWB across time was weaker in children with more severe epilepsy and in those with fewer resources. See Table 6-3 for details.

6.3.4 Conditional Growth Mixture Model

Conditional growth mixture models were tested under various restrictions and models with convergency problems were removed. Results suggested either a 2-class or 3-class no within-class variance model. Ultimately the 2-class model was chosen to best represent the data. A summary of fit statistics for candidate models can be seen in Table 6-4.

In the first class (n=112, 32% of sample), mean EWB was 61.6 at baseline and increased to a mean of 62.0 at 24-months. In the second class (n=235, 68% of sample), mean EWB was 78.7 at baseline and increased to a mean of 79.9 at 24-months. A difference in EWB between classes was significant at each time point

($p<0.001$ for all). Variables impacting the trajectories were the same for both classes: presence of behavioural problems, family demands, and family functioning ($p<0.05$ for all). Estimates for variables in class 1 were approximately twice as large as those in class 2. Concerning the slope, severity of epilepsy, family resources, and an interaction between the two were significant ($p<0.05$ for all) in class 1 but not in class 2. Using logistic regression, class membership was predicted by severity of epilepsy and family resources ($p=0.03$ and $p=0.02$, respectively). A summary of the results is found in Table 6-5.

6.4 Discussion

Our study provides a better understanding of EWB as a *process* through examinations of individual and group-average trajectories. Results from the overall group-average trajectory suggest that children with epilepsy follow a linear trajectory and individuals with no behavioural or cognitive problems, fewer family demands, more family resources, and a higher functioning family will have better EWB post diagnosis. Further, we found EWB changes across time and is impacted by the severity of epilepsy and the family resources of the child.

Our results suggest that using a group-average trajectory to represent all children with epilepsy may not be sufficiently accurate. Rather, we identified two unique trajectories of EWB for children with newly diagnosed epilepsy. While both had minimal increases over time (mean increase of 0.2 points per year for class 1 and 0.6 points per year for class 2), the two classes significantly differed from each other at each time point. The majority of children diagnosed with epilepsy have a favorable EWB and only a subsample of children (32%) experienced consistently

poorer EWB. While the increases within a class are minimal, there are individuals within each class with larger changes in EWB. These individuals are better represented using two classes of trajectories compared to the full sample group trajectory, but unexplained differences within trajectories still exist for both classes. We speculate that, with a larger sample, we would detect and classify these individuals better.

Our results suggest that the presence of behavioural problems, the level of family demands, and family functioning impact an individual's baseline EWB and this holds true regardless of class membership. While it is becoming well established that family factors have an important role in obtaining a good quality of life for children with epilepsy[30,31], our study suggests that the family environment also plays a role in determining membership to a particular trajectory. We found that the single-item Global Assessment of Severity of Epilepsy (GASE) is the only epilepsy-specific information needed to suggest class membership, indicating this measure as a good candidate to collect epilepsy-related information quickly by physicians. The relationship between the family environment and long-term mental health has been examined in other childhood chronic illnesses. Thompson et al. (1994)[32] found that maternal distress predicted psychological symptoms among children with cystic fibrosis on 1-year follow up. Furthermore, studies are consistent that parental overprotection results in decreased child self-control and predicts long term psychological distress in children with chronic illnesses[33].

Our study may also explain why there have been inconsistencies in results across cross-sectional studies. Some studies have suggested that seizure severity

was associated with EWB[34,35] while other studies have not found this to be the case[36,37]. It is possible that seizure severity does not impact EWB until enough time has passed and thus proximity of data collection to diagnosis could account for some inconsistencies. As well, inconsistencies could be due to the proportion of individuals within a sample with poorer EWB at diagnosis. It is possible that severity of seizures impacts EWB in a similar manner as severity of epilepsy, and in our study severity of epilepsy was not associated with baseline EWB but rather was associated with the slope of the trajectory, impacting the magnitude of increase in EWB across time. Furthermore, this was only the case for individuals in class 1, where individuals start at lower levels of EWB.

This study has several strengths. To our knowledge, this is the only study to examine EWB in children with epilepsy across time. Our sample is fairly large which allowed us to conduct the more complex analyses presented here. Our study had good response rates suggesting strong external validity and used a well-established measure to obtain reliable outcomes.

This study also has some limitations. Our sample is based upon parental report, which is not ideal when examining the EWB. Based on the age range of the children and their geographical dispersion across Canada, self-report was not feasible. Because parental depressive symptoms were prevalent in our sample, there is the possibility of their influence on parental reported outcomes. We believe it is unlikely that depressive symptoms influenced mothers' reports of their children's EWB in our study as a previous study using HERQULES data found no influence of maternal depressive symptoms on maternal reported items used to

measure EWB[38]. Secondly, we do not have data on EWB prior to diagnosis, which would prove useful for understanding the full impact a diagnosis with epilepsy has. While our sample is quite large in relation to previous studies of children with epilepsy, it is small in terms of growth mixture modeling. A larger sample and more data points would provide more opportunities to examine complex relationships.

Overall, our study demonstrated that EWB in children with newly diagnosed epilepsy is not a static outcome but rather dynamically changes across time, and that children with epilepsy are not a homogeneous group but rather follow unique trajectories that are different based on both epilepsy-related factors and family factors. It is important that researchers and health care practitioners be aware of these differences when examining a child with epilepsy. It is hoped that by taking account of these differences, it may be possible to alter and improve the trajectories of each child at risk.

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Table 6-1. Child and Parent Characteristics at Baseline.

	Baseline (n=373)
Child Factors	
Age, years	7.5 (2.3)
Male %	52
Seizure type, partial %	61
Prescribed AEDs %	67
Experiencing seizures %	93
Epilepsy severity, GASE	5 (1.2)
Cognitive problems %	20
Behaviour problems %	15
Emotional Well-Being, QOLCE	72.5 (13.2)
Parent Factors	
Age, years	38 (6.1)
Female %	93
Married or living with a partner %	87
Employed %	67
Post-secondary education %	67
Annual household income ≥60,000 %	56
Parental Depression	37.2
Resources, FIRM	50.1 (11.1)
Demands, FILE	9.5 (6.5)
Functioning, APGAR	13.9 (3.8)

For continuous variables, values represent mean (standard deviation).

Table 6-2. Linear Unconditional Latent Growth Model Estimates.

		Estimates	p-value
Means			
	Intercept	72.99 (0.65)	>0.001
	Slope	0.49 (0.17)	0.003
Variances			
	Intercept	121.27 (11.65)	>0.001
	Slope	4.27 (1.08)	>0.001
Covariance			
	Intercept-Slope	-5.06 (2.42)	0.04
Residual Variances			
	Baseline	61.47 (7.52)	>0.001
	6-Months	42.67 (4.91)	>0.001
	12-Months	41.64 (4.74)	>0.001
	24-Months	19.65 (8.87)	0.03
R-Square			
	Baseline	0.66 (0.04)	>0.001
	6-Months	0.73 (0.03)	>0.001
	12-Months	0.74 (0.03)	>0.001
	24-Months	0.88 (0.05)	>0.001

Table 6-3. Linear Conditional Growth Models

		Estimates	p-value
Intercept			
	AED	-1.40 (0.94)	0.14
	Depressive Symptoms	-0.04 (0.06)	0.47
	Behavioural Problems	-7.77 (1.58)	>0.001
	Cognitive Problems	-3.57 (1.52)	0.01
	Family Demands	-0.22 (0.10)	0.02
	Family Functioning	0.76 (0.16)	>0.001
	Family Resources	0.17 (0.07)	0.02
Slope			
	Severity of Epilepsy	0.05 (0.12)	0.71
	Family Resources	0.18 (0.06)	0.004
	Severity of Epilepsy X Family Resources	-0.03 (0.01)	0.003
Covariance			
	Intercept-Slope	-5.71 (2.11)	0.007
Residual Variances			
	Baseline	55.48 (7.04)	>0.001
	6-Months	44.43 (4.98)	>0.001
	12-Months	39.33 (4.53)	>0.001
	24-Months	18.28 (8.27)	0.03
	Intercept	78.57 (8.67)	>0.001
	Slope	3.75 (1.01)	>0.001
R-Square			
	Baseline	0.69 (0.04)	>0.001
	6-Months	0.72 (0.03)	>0.001
	12-Months	0.75 (0.03)	>0.001
	24-Months	0.88 (0.05)	>0.001
	Intercept	0.36 (0.05)	>0.001
	Slope	0.05 (0.03)	0.16

Table 6-4. Conditional Growth Mixture Models

Model	Classes	BIC/aBIC	Entropy	LMR-LRT	
				2LL	p
1. No within-class variance	2	8858.5 /8741.2	0.82	421.8	0.005
	3	8841.9 /8657.9	0.74	139.5	0.04
2. Equal intercept variance, No within-class slope variance	2	8756.6 / 8636.0	0.85	80.8	0.12
	3	8816.6 / 8629.4	0.71	63.6	0.13
3. Equal intercept variance, Equal slope variance	2	8757.3 / 8630.4	0.89	76.6	0.18
	3	8817.1 / 8623.6	0.81	63.1	0.33

Table 6-5. Estimates for the Two-Class Conditional Growth Mixture Model

		Class 1		**Class 2**	
		n=112 (32%)		n=235 (68%)	
		Estimate	p-value	Estimate	p-value
Intercept					
	AED Use	-0.59 (1.45)	0.69	-1.13 (0.75)	0.13
	CESD	0.08 (0.09)	0.37	0.03 (0.05)	0.62
	Behavior Problems	-13.15 (2.06)	0.001	-6.44 (1.61)	0.001
	Cognitive Problems	-1.08 (2.94)	0.71	0.33 (2.68)	0.90
	FILE	-0.52 (0.21)	0.01	-0.26 (0.08)	0.001
	APGAR	1.03 (0.23)	0.001	0.74 (0.18)	0.001
	FIRM	-0.04 (0.11)	0.73	0.05 (0.06)	0.44
Linear Slope					
	GASE	-0.47 (0.25)	0.05	-0.24 (0.16)	0.12
	FIRM	0.25 (0.09)	0.005	-0.08 (0.08)	0.30
	GASE*FIRM	-0.05 (0.02)	0.005	0.01 (0.01)	0.30
Logistic		Estimate	p-value	Odds Ratio	
	AED Use	0.11 (0.28)	0.71	1.11	
	GASE	-0.25 (0.12)	0.03	0.78	
	CESD	0.03 (0.02)	0.19	1.03	
	Behavioural Problems	-0.49 (0.49)	0.32	0.61	
	Cognitive Problems	0.98 (0.65)	0.13	2.67	
	FILE	-0.03 (0.03)	0.31	0.97	
	APGAR	0.03 (0.06)	0.63	1.03	
	FIRM	-0.05 (0.02)	0.02	0.96	

*Class 2 used as reference category for logistic regression estimates

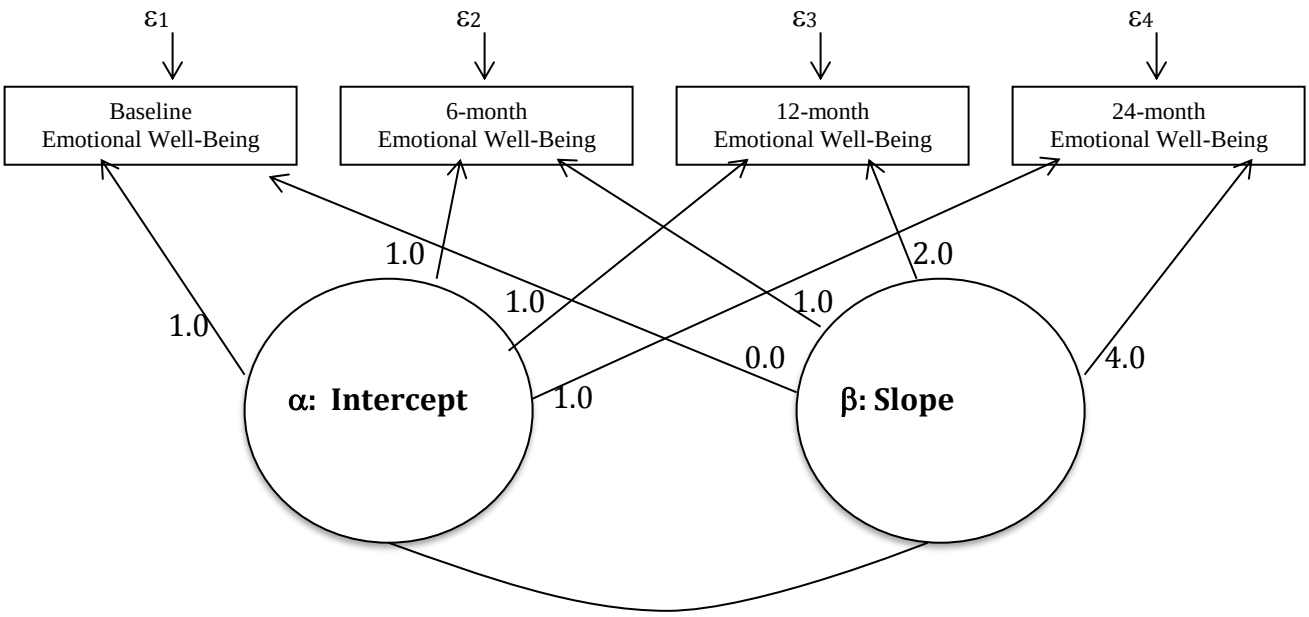

Figure 6-1. Unconditional Linear Growth Model for Emotional Well-Being.

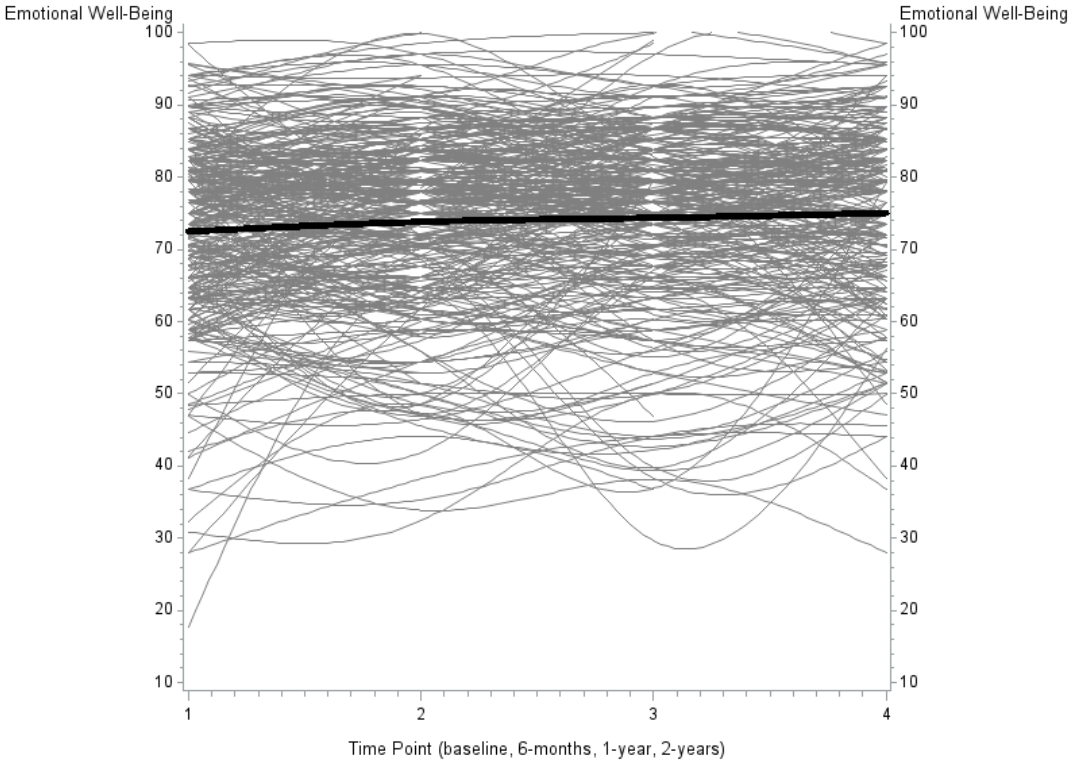

Figure 6-2. Individual trajectories of emotional well-being with bold line representing mean emotional well-being for the entire group.

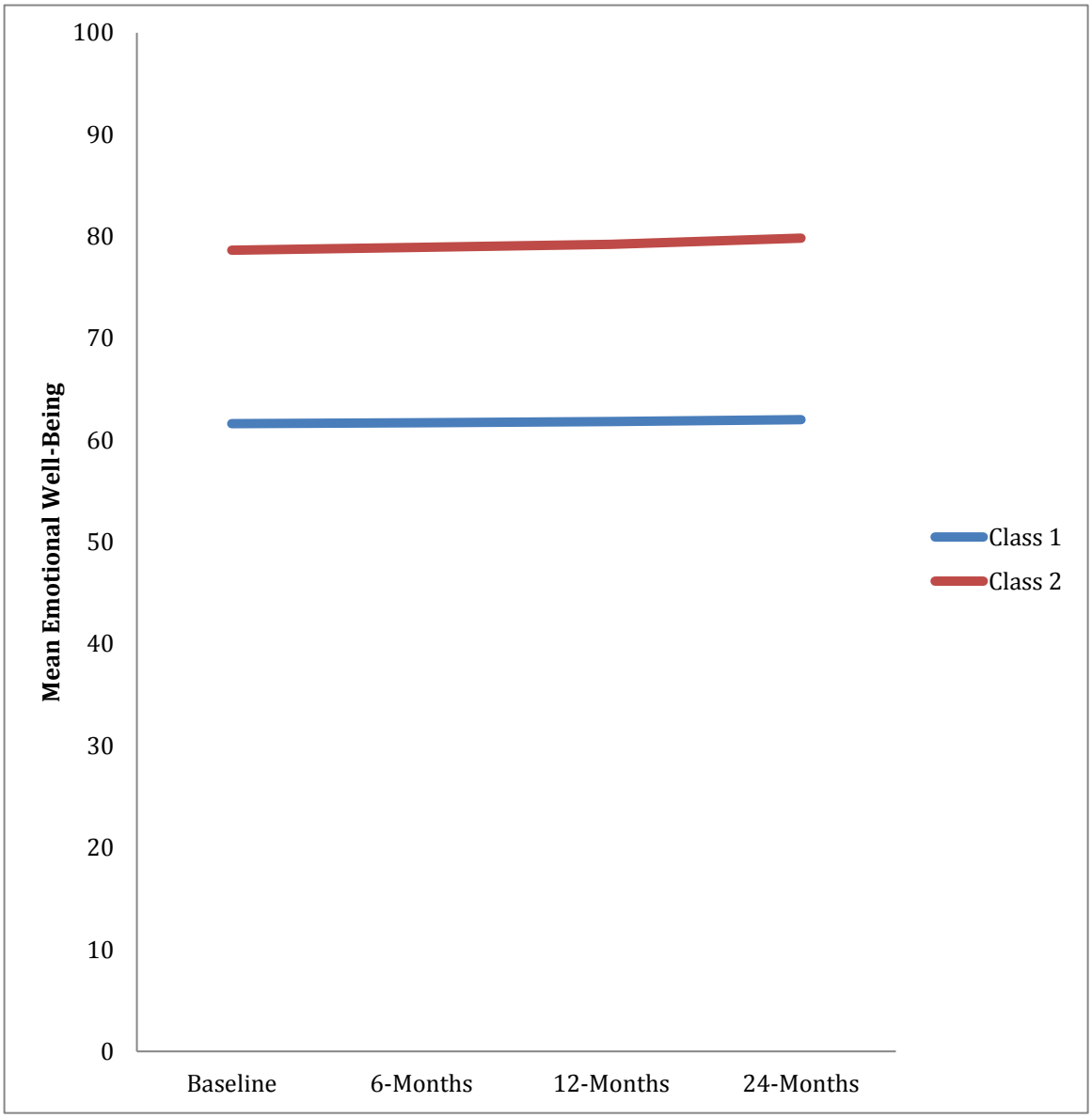

Figure 6-3. Trajectories of emotional well-being across time for the 2-class model.

Chapter Seven: Summary and Discussion

7.1 Introduction

Research suggests that children with epilepsy have significantly poorer emotional well-being (EWB) compared to their healthy peers or children with other conditions. Research has been inconsistent regarding risk factors associated with poor EWB in children with epilepsy and regarding the roles of epilepsy-related factors and family factors on EWB. It remains unclear how the course of EWB changes across time or what factors may impact its course.

This chapter summarizes the findings within the context of previous literature and discusses their potential implications. It also discusses the strengths and weaknesses of this research, as well as suggests possible future research. The overall goals of this thesis research was to further our understanding of EWB in children with newly diagnosed epilepsy and elucidate the role family factors have in the relationship between epilepsy-related factors and EWB. This research investigated whether children with epilepsy are a homogeneous group in regards to EWB or comprise distinct groups with unique needs. By understanding the course of EWB over time and the factors impacting it, interventions to maximize EWB can be developed and evaluated as a step towards optimizing health-related quality of life (HRQL).

7.2 Summary of Key Findings

7.2.1 Emotional Well-Being in Children with Epilepsy: Family Factors as Mediators and Moderators

We assessed which baseline epilepsy-related factors were associated with EWB at twenty-four months post-diagnosis in children with epilepsy. Our analyses were viewed under the lens of the Stress Process, a conceptual framework within which a diagnosis of epilepsy manifests epilepsy-related factors, acting directly or indirectly through family factors, to impact EWB at 24-months post-diagnosis. In this study, family functioning, family demands, and family resources were examined as a possible mediators or moderators.

Our results indicated that the presence of behavioural problems was associated with lower EWB 24-months post-diagnosis in children with epilepsy. Components of the family environment were strongly associated with EWB, and both family functioning and family demands fully mediated the relationship between parental depressive symptoms and EWB. Family resources partially mediated the effects of both family functioning and family demands on EWB. Additionally, an interaction between family resources and the severity of epilepsy suggests family resources as a moderator, where severity of epilepsy had a stronger impact on a child's EWB in families with fewer resources.

While our findings had some similarities to those previously reported, there were some key differences. Previous studies have been inconsistent in their findings regarding epilepsy-related factors, such that some studies found the severity of seizures[1,2] to be associated with EWB while others did not[3,4]. The measure of

severity we employed was overall severity of epilepsy, which takes into account other dimensions of epilepsy in addition to the severity of seizures such as disability associated with epilepsy and side effects of anti-epileptic drugs. Severity of epilepsy was only significant in an interaction with family resources, where severity of epilepsy had less effect on children's EWB in the presence of more resources. It is possible that severity of seizures acts in a similar manner as severity of epilepsy and the discrepancy in previous findings regarding the effect that severity of seizures has on EWB may be due to differences in the set of risk factors included in analyses, differences in the severity of epilepsy of each sample, or differences in the family resources of each sample. It is possible that studies finding severity of seizures to be a significant epilepsy-related factor had samples with fewer family resources. Unfortunately, previous studies that found severity of seizures significantly associated with EWB did not include family factors in their analyses. In our study, we found family factors acted as mediators and moderators, partially reducing the effects of epilepsy-related factors and completely reducing the impact of parental depressive symptoms on EWB. Differences in the set of risk factors included in analyses may also explain differences in results among studies.

In our study, the presence of behavioural problems had the strongest association with EWB in children with epilepsy compared to other epilepsy-related factors. To the best of our knowledge, no previous studies have examined the impact of behavioural problems on EWB thus precluding comparisons between studies.

In our study, family factors were strongly associated with EWB, which is consistent with other reports in the literature. Previous studies found family

functioning and support reduce the risk of behavioural and emotional problems in children with epilepsy[5-8]. While previous literature has not examined the mediation or moderation roles of components of the family environment on EWB in childhood epilepsy, similar effects have been described in examining risk of behavioural problems. One study found parenting styles and stigma partially mediated the effects of seizure type on the risk of behavioural problems[10] and similar effects were found regarding other components of the family environment on the risk of behavioural or emotional problems[10-13]. This is consistent with findings in children with other chronic health conditions as well. Maternal distress has been found to predict psychological symptoms one year later in children with cystic fibrosis[14] and in other studies of chronic illness in children[15,] parental overprotection has been found to consistently result in decreased child self-control and predict poorer long-term psychological well-being due to increases in psychological distress[15]. In one study of childhood epilepsy, the authors hypothesized that the roles of components of the family environment on mental health outcomes are dependent upon the proximity of a particular factor to the child-parent interaction[16] and our results appear to agree with this hypothesis.

As a secondary objective, we examined the consequences of measuring EWB using only negative affect items. We found that estimates of EWB did not significantly differ, but an additional interaction effect was found between family resources and presence of behavioural problems. The presence of behavioural problems had a smaller effect in children with more family resources. Using the full measure, this interaction was significant when not including other epilepsy-related

factors but became nonsignificant when included in the full model. Our results suggest that a balanced measure is important when examining unadjusted results and should be taken into account when examining the results of other studies.

7.2.2 Trajectories of Emotional Well-Being in Children with Epilepsy

We described the course of EWB in children with epilepsy across 24 months post-diagnosis. We identified that two unique linear trajectories best captured the course of EWB and reduced heterogeneity among individuals within a trajectory group. While the same set of epilepsy-related factors and family factors affected the level of EWB at diagnosis between the two groups, individuals with poorer EWB (33% of the sample) were uniquely impacted in their change in EWB across time. We found that for individuals on the poorer emotional well-being trajectory, their change in EWB across time was associated with severity of epilepsy, family resources, and an interaction between the two factors. While changes in EWB across time were minimal, the two trajectories significantly differed in their initial EWB.

Membership to a particular trajectory class was associated with severity of epilepsy and family resources. Severity of epilepsy and family resources may be key factors to target for intervention at the time of diagnosis to maximize a child's probability of following the higher EWB trajectory.

To our knowledge, there are no studies in the literature investigating trajectories of EWB or changes in EWB across time in children with epilepsy. Our results continue to suggest that both behavioural problems and the family environment play important roles in the overall impact a diagnosis of epilepsy can have on a child. Unique to our study, we found that severity of epilepsy was only

associated with changes in EWB across time. It is hoped that as more studies examine the course of EWB, it will be possible to clarify some inconsistencies found in the literature.

7.3 Potential Implications

The overall findings of this thesis suggest that components of the family environment are key in improving EWB in children with epilepsy. We suggest that it would be beneficial for physicians to be aware of this at the time of a diagnosis of epilepsy and to have open dialogue with parents regarding the importance of strengthening both internal and external support structures. Our study builds upon previous research regarding the importance of specific components of the family environment in children with epilepsy and points to potential targets for intervention. In our study we have used a framework for investigating EWB in children with epilepsy that utilizes the stress process. Specifying and examining relationships among epilepsy-related and family factors simultaneously may resolve some inconsistencies found in the literature. This thesis research demonstrates that children with newly diagnosed epilepsy follow different trajectories of EWB based on a set of epilepsy-related and family factors.

While our study found changes in EWB across time were minimal, there is a concern regarding the large variability in baseline EWB. Research consistently shows that early mental health problems predict long-term worse psychosocial and socioeconomic outcomes and that these effects are much stronger than those from childhood physical illness[17]. Given the long-term effects of childhood epilepsy, the importance of intervention is apparent. Interventions need to not only remedy the

physical symptoms of epilepsy but also reduce the psychosocial and socioeconomic costs associated with long-term trajectories of psychological problems. These problems have increasingly important economic costs on the child, where recent studies have shown that individuals experiencing childhood psychological problems have a resultant cost in terms of loss of future earnings of over $500,000 over the life time[18]. These costs are underestimates, as they do not include increased costs or burdens to other members of the family.

Based on our results, we postulate that interventions aimed at improving components of the family environment, especially through improvements in family resources and coping skills, health practitioners may see further improvement in a child's long-term EWB and thus HRQL of a child with newly diagnosed epilepsy. Improvement of the family environment appears to be a key target in order to maximize a child's chance of following a higher EWB trajectory.

7.4 Study Strengths

This thesis research has several strengths that allowed the opportunity to expand on previous research in the field of childhood epilepsy and EWB. First, a strong conceptual framework guided the treatment of factors included and the interpretation of results obtained. To our knowledge, no other study examining EWB in childhood epilepsy has used a conceptual framework to guide analyses or interpretations. The lack of a conceptual framework has likely contributed to inconsistencies in findings in the literature as well as a lack of inclusion of confounders during analyses, and inconsistencies in the measurement of factors. In this thesis research, we utilized the Stress Process Model to examine the

relationship among various stressors and identify possible mediators and moderators. Building upon a strong conceptual framework has focused our analyses to examining the relationships among various factors related to EWB.

A second strength is the quality of the data set analyzed. HERQULES contains a large number of factors related to the family environment and numerous epilepsy-related factors, allowing us the opportunity better examine the impact of each on EWB. Collection of data across twenty-four months post diagnosis allowed us to longitudinally assess changes in EWB. These aspects are a significant improvement on previous research where a smaller set of factors is typically available and analyses have been constrained to only cross-sectional examinations. The HERQULES data set also provided a large sample compared to previous research, allowing us the ability to use more rigorous methods for examining change in EWB across time. While smaller samples have been used in longitudinal studies, growth modeling is regarded as a large sample method[19].

As well, our studies included a number of confounders, the control of which improved our ability to obtain accurate estimates of the association among factors. None of the previous studies reviewed included confounders to adjust estimates. By including confounders in our analyses, we reduced the distortions of the observed associations among the epilepsy-related factors and family factors with EWB, and as a result, reduced the chance of false conclusions. Finally, the data set used in this thesis was collected from across Canada and the results are broadly generalizable. While our study is composed largely of individuals with less severe epilepsy, research suggests that approximately 80% of children with idiopathic epilepsy and

approximately 50% of children with all types of epilepsy will become seizure free[20-23]. As such, our results are likely to be fairly generalizable to children diagnosed with epilepsy between the ages of four and twelve.

7.5 Study Limitations

While this research had multiple strengths, it was not without limitations. Estimates of child EWB were based on parental report and, while it would be ideal to obtain self-report data, the young age and geographical spread of children in our sample across Canada make it difficult to do so. While there are limited studies investigating differences in reported EWB in children with epilepsy based upon who is reporting, research suggests only small differences in estimates were obtained across child, parent, or teacher reporting[24-26]. There is the possibility of information bias in our sample because the proportion of parents reporting parental depressive symptoms is high. We are not as concerned that an information bias occurred in our study because a previous analysis using HERQULES data found no difference in reporting children's outcomes when mothers with depressive symptoms were compared to those without depressive symptoms[27]. Clinical information regarding epilepsy was obtained through a physician report and would not be influenced by parental depressive symptoms. Another possible source of information bias is in the assessment of behavioural and cognitive problems as these were based on neurologists' ratings rather than formal diagnosis. While this information was based on physicians' clinical judgment rather than standardized testing, we are not using this information in order to diagnose a child but rather to understand the general

associations of behavioural problems or cognitive problems on EWB. As such we do not believe this will affect the relationships reported.

Although our sample is relatively large compared to other studies, it is considered small in terms of the complex analyses conducted. In establishment of trajectories of EWB, our results were limited to examining two and three class models. While this may have limited the number of possible classes, we were able to examine the key relationships of interest and there is no guarantee more classes would have resulted in a better fitting model.

Our sample is one of convenience and does not represent true probabilistic sampling. Sampling from the general population was not a feasible approach as it is unlikely to produce a sufficient number of children with epilepsy. Our data set does contain considerable variation though in types of epilepsy and other epilepsy-related characteristics allowing us to examine children with epilepsy across a wide spectrum of characteristics.

Attrition and selection bias may have been an issue in our analyses as it is in all cohort studies. In our study, it is reasonable to assume parents of children with more severe types of epilepsy would be less likely to agree to participate initially. This fact, combined with attrition, likely resulted in a sample of families experiencing fewer burdens. We do not have reason to believe that the loss of individuals across time resulted in biased estimates, as differences in the relationships among family factors and EWB were not significantly different between those individuals who continued in HERQULES and those who were loss to follow up.

Finally, we do not have data on EWB prior to a diagnosis with epilepsy. As a consequence, we are missing a part of the picture in terms of a child's EWB trajectory and are unable to determine whether EWB over time returns to pre-diagnosis levels.

7.6 Future Research

The studies reported in this thesis are a first step toward improving our understanding of EWB in children with newly diagnosed epilepsy. Research on EWB has been limited and to our knowledge, our study is the first to examine EWB longitudinally. While a strong conceptual framework guided our research, having additional data measuring other aspects of the family environment would be beneficial. Specifically, research on the stress process suggests that understanding differences in coping responses and social support among individuals may account for the heterogeneity in stress responses[28-31]. The ability to predict which individuals and their families are likely to respond more poorly to a diagnosis with epilepsy, and understanding the most optimal way to intervene before EWB is severely impacted is important. To do so, we require extensive research in how EWB changes across time and the role of various factors at each time point. While the data used during this thesis provided an opportunity to examine change across time, future research should strive for more data collection points to capture any non-linear trends that may exist in the data. This may result in the identification of additional unique trajectories and more similar individuals within trajectories than we were able to detect in our study.

The long-term goal of this thesis research is to identify targets for possible interventions to improve EWB in children with newly diagnosed epilepsy. While currently no major interventions exist in children with epilepsy, there have been some pilot studies examining interventions to improve HRQL and psychosocial resources of the child such as self-esteem and social confidence. For example, a karate program was shown to improve self-esteem and social confidence, and have a small but non-significant effect of alleviating parental stress, suggesting a structured family intervention program may improve EWB[32]. A psycho-educational structured group intervention found a positive trend towards improved quality of life through the incorporation of cognitive-behavioural strategies for both adolescents and their parents[33]. To our knowledge, there have not been any evaluations of interventions focusing on improving the family environment, coping skills, or social support structures with the intent to improve EWB or HRQL in children with epilepsy. There have been interventions in other childhood illnesses that found success in the strengthening of coping skills[34-35], family functioning[36-37], and social support structures of the family[38-39], and it is believed that these improvements have a positive impact on the child's health across a variety of outcomes[40]. Many interventions for children with chronic illnesses target parents or siblings but results are mixed in their effectiveness, with the most successful results coming from interventions utilizing cognitive behavioural therapy[41]. Cognitive behavioural therapy has been consistently shown to improve depression and anxiety at a rate of approximately 50%[42]. Still, few interventions attempt to improve long-term outcomes through strengthening the family rather than treating a child's specific

problem. The creation, implementation, and evaluation of a targeted intervention using a mix of cognitive behavioural therapy and social support training to strengthen the coping skills of the family would be a strong next step in improving EWB and HRQL in childhood epilepsy.

7.7 Conclusions

Epilepsy is the most common disease of the brain in children, with the prevalence in Canada estimated to be 2.5-4.4 cases per 1000[43]. With estimates of up to 10.5 million children with epilepsy worldwide[44] and a high risk of psychosocial problems[44-47], a greater understanding of the factors impacting both EWB at diagnosis and the course of EWB across time becomes increasingly critical.

This thesis makes a significant contribution to the field of childhood epilepsy by elucidating the role both epilepsy-related and family factors on their association with EWB. We have demonstrated that epilepsy-related factors and family factors act in a sequential manner and in certain cases, interact with each other, resulting in a complex relationship with EWB. Our findings stress the importance of strengthening the family environment during the discussion of treatment strategies both at diagnosis and across the treatment timeline. As children with epilepsy are not a homogenous group, a subset of children and families would benefit from additional resources to reduce the risk of poor EWB.

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Appendix A: Data Collection

The data used in this thesis research came from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES). The primary objective of HERQULES was to describe the course and identify determinants of health-related quality of life over a two-year period.

Study Design

HERQULES is a multi-centre, prospective cohort study where children with newly-diagnosed epilepsy, aged 4-12 years old from across Canada, were followed for 24 months. A two-stage clustered sampling design was used in order to recruit both paediatric neurologists and families to participate. Over the 24-month period, data were collected at four times: baseline (as near diagnosis as possible), six, 12, and 24 months later. The specific time-points were selected based on a priori considerations, as there are no known optimal times for capturing HRQL information. Three assessments were completed in the first year because HERQULES researchers hypothesized that during this period family and epilepsy factors would be most dynamic, and one assessment during the second year when it was expected that factors would have become more stable.

Sample Characteristics

The study population is children in Canada with newly-diagnosed epilepsy who are receiving care from a paediatric neurologist. Children and their families were recruited prospectively over a 36-month period from April 2004 to April 2007. Parents/caregivers of each eligible child were approached for participation in the

HERQULES study based on the following criteria. Inclusion criteria were: 1) new case of epilepsy (two or more unprovoked seizures) seen for the first time by a participating paediatric neurologist within the collection period; 2) diagnosed between the ages of 4-12 years; and, 3) parent/caregivers primarily responsible for the child's care for at least six months and would be continuing for the duration of the study. Additionally, children with newly diagnosed epilepsy but whom had a prior history of neonatal seizures were included if medication was removed by six weeks of age and seizures did not reoccur. Exclusion criteria were: 1) diagnosis of epilepsy had been previously confirmed; 2) diagnosed with other progressive or degenerative neurological disorder; 3) diagnosed with other major co-morbid non-neurological disorders that would impact health-related quality of life; 4) insufficient English language skills.

Recruitment:

Recruitment into HERQULES study occurred in two stages. In the first stage, all currently practicing paediatric neurologists in Canada who cared for children with epilepsy were invited to participate in the study. In the second stage, participating neurologists identified all children meeting inclusion criteria and neurologist's staff approached these children's families to introduce the HERQULES study. Families who were identified as eligible and potentially interested were mailed a letter of information describing HERQULES and requirements for participation, and within a few days family members were contacted by HERQULES staff.

Physician Recruitment:

All practicing paediatric neurologists in Canada were approached for participation in HERQULES. To identify practicing paediatric neurologists, the current membership list of the Canadian Association of Child Neurology (CACN) was used and established a sampling frame. A total of 103 paediatric neurologists were identified from CACN. To ensure completeness of the sample, a small number of members reviewed the current list and added names of individuals whom were missing and removed the names of members who were no longer in practice. These members reduced the sampling frame to a total of 72 eligible paediatric neurologists, each who were contacted and agreed to participate. Of these, a total of 53 (74%) were successful in recruiting participants into HERQULES. Each paediatric neurologist was provided study materials, an overview of the study, physician report forms, study timelines, inclusion/exclusion criteria, and a token of appreciation. In addition to participation in identifying eligible families, paediatric neurologists provided clinical information regarding participating children's epilepsy at each collection point. In an attempt to minimize loss of data, paediatric neurologists were sent reports every six weeks listing which children's clinical information was not yet received by HERQULES staff.

Family Recruitment:

Paediatric neurologist and their staff approached parents with information regarding HERQULES. If parents were interested in participating, a release of information form would be signed by the parent and faxed to HERQULES office, allowing HERQULES staff to contact and provide additional information. Interested

parents were sent letters of information and were contacted by phone to further address any questions and finalize participation. Each family was asked to complete a 45-60 minute questionnaire during each data collection period. Questionnaires were mailed to participating families at entry to study and subsequently at 6, 12, and 24-months. Using the Flesch-Kincaid Grade score, questionnaires were deemed at requiring a grade seven grade for comprehension. Participating families received a small token of appreciation ($5.00) with each questionnaire. At the final data collection point, families were asked if they would like a summary of HERQULES results.

The HERQULES study used the Tailored Design Method in order to maximize the quantity of responses and participation rate while maintaining the quality of responses. A total of 456 families were identified as eligible and 443 (97%) agreed to receive information regarding HERQULES. The baseline questionnaire was completed by a total of 373 parents (82%) and the 24-month questionnaire was completed by a total of 282 parents (76% retained from baseline to 24-month). The HERQULES study retained 62% of all possible participants and each proceeding time point had a participation rate 90% or greater (see figure A-1).

Data Quality Assurance:

Paediatric neurologists recorded clinical epilepsy information at each study site and mailed or faxed completed forms to the HERQULES office. Parents provided child and family information and mailed completed questionnaires to the HERQULES office. HERQULES staff then examined each questionnaire and removed identifying information and ensured completion of all sections. If sections were

missing, HERQULES staff would contact parents and sent the missing sections for completion. HERQULES staff entered data using the Statistical Package for the Social Sciences (SPSS, Windows build 16, SPSS Inc., Chicago, IL). HERQULES staff reviewed any responses not compliant with response options and all decisions regarding coding were recorded in a data log. Data verification was provided by HERQULES staff who had not entered the individuals data initially. All questionnaires were electronically archived and questionnaires that could not be legibly scanned were archived in physical paper form.

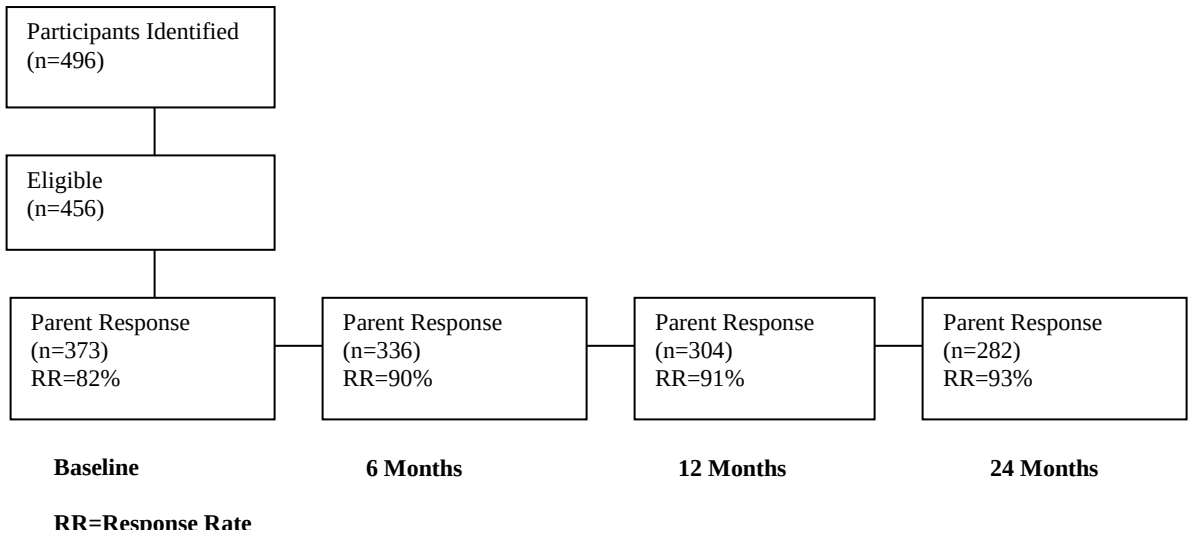

Figure A-1. Participant Recruitment and Retention.

Appendix B: Ethics Approval

Ethical approval for the original HERQULES protocol was obtained from the Research Ethics Board at Western University and all appropriate ethics boards across the country. Approval forms can be provided upon request.

Appendix C: Measurement

Measures used in the study are summarized in Table C-1. Parental reported measures are described first followed by physician reported measures. A modified version of the parent questionnaire containing only items used in this doctoral research and the physician form completed by neurologists are found in Appendix D.

Emotional Well-Being:

HERQULES employed the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire; an epilepsy-related measure for parental report of children aged 4 to 18 years[1]. The QOLCE contains an Emotional Well-Being subscale, providing the opportunity to focus on emotional well-being as an outcome. This study will use the emotional well-being subscale from a reduced-form version of the QOLCE, QOLCE-55, created by Goodwin et al. (2015; see Chapter 4). The Emotional Well-Being subscale contains 17 items, with 12 items measuring negative affect and 5 items measuring positive affect. Items are rated on a five-point Likert scale and scores are transformed to range from zero to 100, with higher scores representing better functioning[1]. The Emotional Well-Being subscale has been shown to be reliable , with a Cronbach's alpha of 0.88 in HERQULES.

Parental Depression:

Parental depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D)[2]. The CES-D is a 20-item self-report scale measuring depressive symptoms in the general adult population over

the past four weeks[2]. The CES-D uses a four-point Likert scale with responses ranging from 0 to 3 on the frequency of symptoms experienced, with 0= "rarely or none of the time" (less than one day) to 3= "most or all of the time" (5 to 7 days)[2]. The total score ranges from 0 to 60, with greater scores indicating greater depressive symptoms[2]. A score of 16 or greater indicates an individual who is likely at risk for being clinically depressed. The CES-D has been found to have good construct validity[3-6] and able to discriminate between psychiatric patients treated for depression and other psychiatric patients[4]. The CES-D has been used to examine depressive symptoms among chronically ill individuals and their families[7-9]. The CES-D has been found reliable with Cronbach's alpha ranging from 0.75-0.80 across the four time-points in the HERQULES sample.

Family Functioning:

Family functioning was assessed using the Family Adaptability, Partnership, Growth, Affection, and Resolve scale[10]. The Family APGAR measures family functioning by through items assessing family member's self-reported satisfaction with each of five domains: adaptation, partnership, growth, affection, and resolve. The Family APGAR is a 5-item measure using a three-point Likert response scale ranging from 0 to 2. A total score is calculated by summing the scores of each item, with higher scores indicating higher satisfaction with family functioning[10]. The Family APGAR has been found to be reliable, with Cronbach's alpha ranging from 0.86-0.89 in HERQULES.

Family Demands:

Family demands were assessed using the Family Inventory of Life Events and Changes (FILE)[11]. The FILE measures family demands in terms of the number of life events experienced by any family member over the previous year, assuming that a change in one family member may also affect other family members and affect the family unit as a whole[11]. The FILE is a 71-item measure grouped into nine scales by type of event[11]. The total score is computed by summing all "yes" responses (value of 1), providing both total subscale scores and a total score. The FILE has been shown to have discriminate validity by differentiating between families with low and high income ($p < 0.01$)[12]. The FILE has been found to be reliable, with a Cronbach's alpha ranging from 0.98-0.99 in HERQULES.

Family Resources:

Available family resources to aid families' adaptation to stressful events was assessed using the Family Inventory of Resources for Management (FIRM)[13]. The FIRM contains 68-items using four subscales[13]. The HERQULES study used two subscales, family mastery and health and extended family social support, which have been found to be associated with behavioural problems in childhood epilepsy[14]. The family mastery and health subscale includes 20 items and the extended family social support subscale includes 4 items. Item scores ranges from 0 to 3 and a total score is calculated by summing scores on all items. The FIRM has been found to be reliable, with a Cronbach's alpha ranging from 0.91-0.93 for the family mastery and health subscale and 0.44-0.54 for the extended family social support subscale in HERQULES.

Demographics:

Demographic characteristics of families, including parent's age, education, marital status, employment status, child sex, and household income were also collected. These items were adapted from previously successful studies.

Epilepsy Factors:

Physicians reported clinical information regarding epilepsy through the completion of a two-page physician form. Severity of epilepsy was classified using the Global Assessment of Severity of Epilepsy (GASE), a single-item measure developed for neurologists to rate overall severity of epilepsy using a seven-point scale with scores ranging from 1 (not severe at all) to 7 (extremely severe)[15]. The GASE requires neurologists to make an assessment based on their clinical experience when answering the following question: "Taking into account all aspects of this patient's epilepsy, how would you rate its severity now?" Both construct and convergent validity were assessed and found to be adequate[15]. Inter-rater reliability and test-retest reliability were found to be good; weighted kappa values for the two raters were 0.90 (95% CI: 0.82, 0.98) and 0.95 (95% CI: 0.91, 0.98), with a Spearman rank correlation between times 1 and 2 of 0.94 (95% CI: 0.89, 0.96)[15]. Neurologists recorded types of epilepsy syndrome, which were coded in two ways using the ILAE Classification and Terminology[16,17]: broadly by generalized or partial, and by specific subtype (primary generalized, absence, simple/complex partial, secondary generalized, BECRS, BECRS and secondary generalized, or undetermined). Medication use was measured as the number of antiepileptic drugs prescribed currently and total. Neurologists also were asked to provide an educated

assessment based on their clinical experience whether children had behavioural or cognitive problems and to indicate this on four-point and five-point Likert scales, with lower scores representing milder problems.

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Table C-1: Summary of Measures used in HERQULES.

Parental Report Measures		
Characteristic	**Measure**	**Description**
Emotional Well-Being	Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55); Emotional Well-Being Subscale (Goodwin et al. 2015, see Appendix D).	• 17-item subscale. • 12 items measuring Negative Affect. • 5 items measuring Positive Affect. • Five-point LIKERT scale (1-5) with overall scores transformed to 0-100. • High scores represent high emotional well-being.
Parental Depression	Centre for Epidemiological Studies Depression Scale	• 20-item scale, with a total score of 0 to 60. • Four-point LIKERT scale (0-3): 0=rarely or none of the time to 3=most or all of the time. • Scores greater than 16 indicate at risk for clinical depression.
Family Factors	Family Inventory of Life Events and Changes	• 71-item measure over 9 subscales. • Yes or No item response options • Total score for each subscale and for the entire measure are obtained by summing the response options.
	Family Adaptability, Partnership, Growth, Affection, and Resolve scale	• 5-item measure. • 0 to 4 response options (0=never to 4=always)
	Family Inventory of Resources for Management	• Two subscales used: Family Mastery and Health, 20-items; Extended Family Social Support, 4-items. • Response options 0=Not at all to 3=Very well. • Total scores are obtained by summing all items.
Demographics	Parent-Report Child Questionnaire	• Parent age • Work Status: Employed, Not Employed • Highest level of Education: Less than

		8 years, 8-12 years, Completed high school, Completed vocational school, Completed college or university, Completed graduate school. • Marital Status: Married, Widowed, Divorced, Separated, Remarried, Never married • Household Income: Less than $10 000, $10 000-$19 999, $20 000- $29 999, $30 000-$39 999, $40 000-$49 999, $50 000-$59 999, $60 000-$69 999, $70 000-$79 999, $80 000-$89 999, $90 000-$99 999, $100 000 or more
Physician Report Measures		
Epilepsy Characteristics	Physician form contained a series of items drawn from previous studies.	• Seizure type and Epilepsy syndrome: broadly by generalized or partial, and by specific subtype (primary generalized, absence, simple/complex partial, secondary generalized, BECRS, BECRS and secondary generalized, or undetermined. • Number of anti-epileptic drugs currently and total. • Behavioural problems (0= none to 3=severe) • Cognitive problems (0=none to 4=severe)
	Global Assessment of Severity of Epilepsy Scale	• Severity of epilepsy (1=none to 7=extremely severe).

Appendix D: Study Package – Questions used in Dissertation

Epilepsy-Related Characteristics:

PHYSICIAN FORM

Patient's Date of Birth (dd/mm/yy): _____ Site #:_____

Please answer the following questions based on information from this patient's most recent visit and return upon completion

1. Date of patient's last visit (dd/mm/yy): _____ or Date of Telephone F/U (dd/mm/yy)_____

2. Date form completed (dd/mm/yy): _____

If information for 3 thru 7 is unchanged from baseline (diagnosis) visit, please check here and proceed to 8. ☐

3. Seizure type(s): 1) _____ 2)_____

   3)_____ 4)_____

4. Epilepsy syndrome: _____

5. Convulsive status epilepticus:
   ☐ No
   ☐ Yes

6. Exclusive nocturnal seizures:
   ☐ No
   ☐ Yes

7. Age of first seizure (excluding febrile seizure): _____ yrs

8. Does this patient have any family with epilepsy?
   ☐ No
   ☐ Yes

9. Number of AEDs currently: _____

10. Number of AEDs total: _____

11. Is this patient of school age?
    ☐ No

☐ Yes → Grade: ___ ☐ regular class ☐ regular class with resource ☐ special class

12. Does the patient have behavioural problems?
☐ No (normal)
☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

13. Does the patient have cognitive problems?
☐ No (normal)
☐ Yes → Please check one: ☐ borderline ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

14. Does this patient have motor problems?
☐ No
☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

16. Taking into account all aspects of this patient's epilepsy, how would you rate its severity at his/her last visit? Please check <u>one</u> answer.

☐ Extremely severe
☐ Very severe
☐ Quite severe
☐ Moderately severe
☐ Somewhat severe
☐ A little severe
☐ Not at all severe

17. Rate the following aspects of this patient's epilepsy at his/her last visit.

Check <u>one box</u> using the following 7-point scale:
1 = none or never
7 = extremely frequent, severe or high

	1	2	3	4	5	6	7
Frequency of seizures							
Intensity of seizures							
Falls or injuries during seizures							
Severity of post-ictal period							
Amount of antiepileptic drugs							
Side effects of antiepileptic drugs							
Interference of epilepsy or drugs with daily activities							

Child and Family Characteristics:

Parents' Questionnaire

INSTRUCTIONS

1. Most of the questions in this booklet ask about your child's health and well-being. A few of the questions ask about your own health and well-being. Your individual answers will remain strictly confidential.

2. Answer questions by checking the appropriate box (☐ Yes ☐ No ☐ Don't know) or circling the appropriate number.

3. Certain questions may look alike but each one is different. Some questions may ask about problems that your child does not have. Please try to answer each question as it is important for us to know when your child does not have these problems.

4. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can. Write any comments you may have on the page beside the question.

CHILD EMOTIONAL WELL-BEING

Below is a list that describes how your child might feel in general.

1.4. During the past 4 weeks, how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not applicable
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt happy?	☐	☐	☐	☐	☐	☐
c. wished s/he was dead?	☐	☐	☐	☐	☐	☐
d. felt frustrated?	☐	☐	☐	☐	☐	☐
e. worried a lot?	☐	☐	☐	☐	☐	☐
f. felt confident?	☐	☐	☐	☐	☐	☐
g. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
h. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
i. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
j. felt valued?	☐	☐	☐	☐	☐	☐
k. felt no one cared?	☐	☐	☐	☐	☐	☐

Below are statements that describe some children's behaviour.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.
1.13. Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
b. angered easily	☐	☐	☐	☐	☐	☐
c. hit or attacked people	☐	☐	☐	☐	☐	☐
d. swore in public	☐	☐	☐	☐	☐	☐
e. was obedient	☐	☐	☐	☐	☐	☐
r. demanded a lot of attention	☐	☐	☐	☐	☐	☐

FAMILY RESOURCES:

3.1. The next set of questions asks about what social, psychological, community and financial resources families believe they have available to them in the management of family life. To complete this inventory you are asked to read the list of "Family Statements" one at a time. In each statement, "family" means your immediate family (mother and/or father and children.) Then ask yourself: *"How well does the statement describe our family situation?"*

Then make your decision by circling one of the following:

0 = Not At All This statement does not describe our family situation. This does not happen in our family.
1 = Minimally This statement describes our family situation only slightly. Our family may be like this once in a while.
2 = Moderately This statement describes our family situation fairly well. Our family is like this some of the time.
3 = Very Well This statement describes our family very accurately. Our family is like this most of the time.

Please read and record your decision for each of the statements below.

Family Statements:	**Not at all**	**Minimally**	**Moderately**	**Very Well**
a. Being physically tired much of the time is a problem in our family	0	1	2	3
b. We have to nag each other to get things done	0	1	2	3
c. We do not plan too far ahead because many things turn out to be a matter of good or bad luck anyway	0	1	2	3
d. Having only one person in the family earning money is (or would be) a problem in our family	0	1	2	3
e. It seems that members of our family take each other for granted	0	1	2	3
f. Sometimes we feel we don't have enough control over the direction our lives are taking	0	1	2	3
g. Certain members of our family do all the giving, while others do all the taking	0	1	2	3
h. We seem to put off making decisions	0	1	2	3
i. Our family is under a lot of emotional stress	0	1	2	3
j. Many things seem to interfere with family members being able to share concerns	0	1	2	3
k. Most of the money decisions are made by only one person in our family	0	1	2	3
l. It seems that we have more illness (colds, flu, etc.) in our family than other people do	0	1	2	3
m. In our family some members have many responsibilities while others don't have enough	0	1	2	3
n. It is upsetting to our family when things don't work out as planned	0	1	2	3
o. Being sad or "down" is a problem in our family	0	1	2	3
p. It is hard to get family members to cooperate with each other	0	1	2	3
q. Many times we feel we have little influence over the things that happen to us	0	1	2	3
r. We have the same problems over and over – we don't seem to learn from past mistakes	0	1	2	3

Family Statements:	**Not at all**	**Minimally**	**Moderately**	**Very Well**
s. There are things at home we need to do that we don't seem to get done	0	1	2	3
t. We seem to be so involved with work and/or school activities that we don't spend enough time together as a family	0	1	2	3
u. Our relatives seem to take from us, but give little in return	0	1	2	3
v. We try to keep in touch with our relatives as much as possible	0	1	2	3
w. Our relative(s) are willing to listen to your problems	0	1	2	3
x. Our relatives do and say things that make us feel appreciated	0	1	2	3

FAMILY DEMANDS:

4.1. Over their life cycle, all families experience many changes as a result of normal growth and development of members and due to external circumstances. The following list of family life changes can happen in a family at any time. Because family members are connected to each other in some way, a life change for any one member affects all the other persons in the family to some degree.

*"**FAMILY**" means a group of two or more persons living together who are related by blood, marriage or adoption. This includes persons who live with you and to whom you have a long term commitment.*

Please read each family life change and decide whether it happened to any member of your family - **including you** - during the past 12 months and check **Yes** or **No**.

Did the change happen in your family:	During the Last 12 Months **Yes**	**No**	**Score**
I. Intrafamily Strains			
a. Increase of husband/father's time away from family			46
b. Increase of wife/mother's time away from family			51
c. A member appears to have emotional problems			58
d. A member appears to depend on alcohol or drugs			66
e. Increase in conflict between husband and wife			53
f. Increase in arguments between parent(s) and child(ren)			45
g. Increase in conflict among children in the family			48
h. Increased difficulty in managing teenage child(ren)			55
i. Increased difficulty in managing school age child(ren) (6-12 yrs)			39
j. Increased difficulty in managing preschool age child(ren) (2.5-6 yrs)			36
k. Increased difficulty in managing toddler(s) (1-2.5 yrs)			36
l. Increased difficulty in managing infant(s) (0-1 yr)			35
m. Increase in the amount of "outside activities" which the children are involved in			25
n. Increased disagreement about a member's friends or activities			35

Did the change happen in your family:	During the Last 12 Months **Yes**	**No**	**Score**
o. Increase in the number of problems or issues which don't get resolved			45
p. Increase in the number of tasks or chores which don't get done			35
q. Increased conflict with in-laws or relatives			40
II. Marital Strains			
a. Spouse/parent was separated or divorced			79
b. Spouse/parent had an "affair"			68
c. Increased difficulty in resolving issues with a "former" or separated spouse			47
d. Increased difficulty with sexual relationship between husband and wife			58
III. Pregnancy and Childbearing Strains			
a. Spouse had unwanted or difficulty pregnancy			45
b. An unmarried member became pregnant			65
c. A member had an abortion			50
d. A member gave birth to or adopted a child			50
IV. Finance and Business Strains			
a. Took out a loan or refinanced a loan to cover increased expenses			29
b. Went on welfare			55
c. Change in conditions (economic, political, weather) which hurts the family investments			41
d. Change in agriculture market, stock market, or land values which hurts family investments and/or income			43
e. A member started a new business			50
f. Purchased or built a home			41
g. A member purchased a car or other major item			19
h. Increased financial debts due to over-use of credit cards			31
i. Increased strain on family "money" for medical/dental expenses			23
j. Increased strain on family "money" for food, clothing, energy, home care			21
k. Increased strain on family "money" for child(ren)'s education			22
l. Delay in receiving child support or alimony payments			41
V. Work-Family Transitions and Strains			
a. A member changed to a new job/career			40
b. A member lost or quit a job			55
c. A member retired from work			48
d. A member started or returned to work			41
e. A member stopped working for extended period (e.g., laid off, leave of absence, strike)			51
f. Decrease in satisfaction with job/career			45
g. A member had increased difficulty with people at work			32
h. A member was promoted at work or given more responsibilities			40
i. Family moved to a new home/apartment			43

Did the change happen in your family:	During the Last 12 Months **Yes**	**No**	**Score**
j. A child/adolescent member changed to a new school			24
VI. Illness and Family "Care" Strains			
a. Parent/spouse became seriously ill or injured			44
b. Child became seriously ill or injured			35
c. Close relative or friend of the family became seriously ill			44
d. A member became physically disabled or chronically ill			73
e. Increased difficulty in managing a chronically ill or disabled member			58
f. Member or close relative was committed to an institution or nursing home			44
g. Increased responsibility to provide direct care or financial help to husband's and/or wife's parents			47
h. Experienced difficulty in arranging for satisfactory child care			40
VII. Losses			
a. A parent/spouse died			98
b. A child member died			99
c. Death of husband's or wife's parent or close relative			48
d. Close friend of the family died			47
e. Married son or daughter was separated or divorced			58
f. A member "broke up" a relationship with a close friend			35
VIII. Transitions "In and Out"			
a. A member was married			42
b. Young adult member left home			43
c. Young adult member began college (or post high school training)			28
d. A member moved back home or a new person moved into the household			42
e. A parent/spouse started school (or training program) after being away from school for a long time			38
IX. Family Legal Violations			
a. A member went to jail or juvenile detention			68
b. A member was picked up by police or arrested			57
c. A member ran away from home			61
d. A member dropped out of school or was suspended from school			38

FAMILY FUNCTIONING:

5.1. Now we would ask that you think about the following and check the answer that best describes how you feel most of the time. Please be honest.

a) When something is bothering me, I can ask my family for help.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

b) I like the way my family talks things over and shares problems with me.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

c) I like how my family lets me try new things I want to do.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

d) I like what my family does when I feel mad, happy, or loving.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

e) I like how my family and I share time together.

☐	☐	☐	☐	☐
Never	Hardly	Some of the time	Almost always	Always

PARENTAL DEPRESSION:

6.1. Now we'd like to ask some questions about you. Please read these sentences that say something about how people sometimes feel and circle the number of the category on this page that best indicates how often you have felt this way in the past 7 days.

0. Rarely or none of the time (less than one day)
1. Some or a little of the time (1-2 days)
2. Occasionally or a moderate amount of time (3-4 days)
3. Most or all of the time (5-7 days)

During the past seven days:

a)	I was bothered by things that usually don't bother me.	0	1	2	3
b)	I did not feel like eating; my appetite was poor.	0	1	2	3
c)	I felt that I could not shake off the blues even with help from my family or friends.	0	1	2	3
d)	I felt that I was just as good as other people.	0	1	2	3
e)	I had trouble keeping my mind on what I was doing.	0	1	2	3
f)	I felt depressed.	0	1	2	3
g)	I felt that everything I did was an effort.	0	1	2	3
h)	I felt hopeful about the future.	0	1	2	3
i)	I thought my life had been a failure.	0	1	2	3
j)	I felt fearful.	0	1	2	3
k)	My sleep was restless.	0	1	2	3
l)	I was happy.	0	1	2	3
m)	I talked less than usual.	0	1	2	3
n)	I felt lonely.	0	1	2	3
o)	People were unfriendly.	0	1	2	3
p)	I enjoyed life.	0	1	2	3
q)	I had crying spells.	0	1	2	3
r)	I felt sad.	0	1	2	3
s)	I felt that people dislike me.	0	1	2	3
t)	I could not get "going".	0	1	2	3

FAMILY DEMOGRAPHIC QUESTIONS:

These final few questions ask about your child and his/her family.

8.17. **Is your child:**

☐ Male ☐ Female

8.18. **What is your child's date of birth?**

☐☐ / ☐☐ / ☐☐
DAY MONTH YEAR

8.19. **Who lives with your child currently?**

Person	Their relationship to your child	Their Age	Their sex
1			☐ Male ☐ Female
2			☐ Male ☐ Female
3			☐ Male ☐ Female
4			☐ Male ☐ Female
5			☐ Male ☐ Female
6			☐ Male ☐ Female
7			☐ Male ☐ Female
8			☐ Male ☐ Female

8.20. **Is anyone helping you to complete this questionnaire?**

→

☐ No ☐ Yes

If yes, who is helping you:
☐ Your spouse/partner
☐ Your child

→

☐ Other

If other, please specify:

_____

8.21. **Are you:**

☐ Male ☐ Female

8.22. **What is your date of birth?**

☐☐ / ☐☐ / ☐☐
DAY MONTH YEAR

8.23. **Which of the following best describes your current work status?** (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for "other" reasons	Looking for work outside the home	Working full or part-time (either outside the home or at a home-based business	Full time homemaker	Student

8.24. **What is your relationship to this child?** (check one box only)

☐	☐	☐	☐	☐	☐
Biological parent	Step parent	Foster parent	Adoptive parent	Guardian	Other (please explain on the line below)

8.25. **What is the highest grade of school you have completed?**

☐ less than 8 years
☐ 8-12 years
☐ completed high school
☐ completed vocational/technical training
☐ completed college/university
☐ completed graduate school

8.26. **What is your current marital status?** (check one box only)

☐	☐	☐	☐	☐	☐
Married	Widowed	Divorced	Separated	Remarried	Never married

8.27. **Are you currently living with a spouse or partner?**

☐ Yes ☐ No → If no, go to question 8.30.

8.28. **Which of the following best describes your spouse's/partner's current work status?** (check one box only)

☐	☐	☐	☐	☐	☐
Not working due to my child's health	Not working for "other" reasons	Looking for work outside the home	Working full or part-time (either outside the home or at a home-based business	Full time homemaker	Student

8.29 **What is the highest grade of school your spouse/partner has completed?**

☐ less than 8 years
☐ 8-12 years
☐ completed high school
☐ completed vocational/technical training
☐ completed college/university
☐ completed graduate school

The next two questions will allow us to compare your family's health to that of other people in the study who are similar to you.

8.30. **In which category is your total yearly household income before taxes?** (check one box only)

☐ Less than $10,000

☐ $10,000 - $19,999

☐ $20,000 - $29,999

☐ $30,000 - $39,999

☐ $40,000 - $49,999

☐ $50,000 - $59,999

☐ $60,000 - $69,999

☐ $70,000 - $79,999

☐ $80,000 - $89,999

☐ $90,000 - $99,999

☐ $100,000 or more

☐ Don't know

8.31. **Thinking about your total family income, from which sources did your family receive income during the past year?** (check all that apply)

- ☐ Wages and salaries
- ☐ Income from self-employment
- ☐ Family allowance (baby bonus)
- ☐ Unemployment insurance or strike pay
- ☐ Worker's compensation
- ☐ Old Age Security, Guaranteed Income Supplement, Canada or Quebec Pension Plan, Retirement Pension Plan, Super-annuation
- ☐ Dividends and interest on bonds, deposits, and saving certificates
- ☐ Other government sources such as welfare, mother's allowance, etc.
- ☐ Other sources(s), please specify: _____

8.32. **How long ago was your child *first* diagnosed with epilepsy?**

_____ Months ago or _____ Weeks ago

8.33. **Who *first* diagnosed your child with epilepsy?** (check one box only)

- ☐ Family Physician
- ☐ Neurologist
- ☐ Pediatrician
- ☐ Other (please specify) _____

8.34. **Did the doctor who first diagnosed your child with epilepsy prescribe any medications for seizures?**

- ☐ Yes
- ☐ No

8.35. **DATE THIS QUESTIONNAIRE WAS COMPLETED:**

☐☐ / ☐☐ / ☐☐

Appendix E: Sample Characteristics, Missing Data, Treatment of Outliers, and Model Diagnostics

1. Sample Characteristics

Characteristics of the sample can be found in Tables E-1 and E-2. Children in general had low severity of epilepsy, had few behavioural or cognitive problems and had moderately high emotional well-being. Children primarily had partial seizures and were on a single AED medication. Families were financially well-off, had received post-secondary education, and had good functioning, resources, and low family demands/stresses.

The amount of attrition over the 24-month study was low, with 75.6% of the sample remaining by the end of the 24-month study period. A loss of 91 individuals occurred across the study (37 lost between baseline and 6-months; 32 lost between 6-months and 12-months; 22 lost between 12-months and 24-months). Those who had not completed the emotional well-being measure in at least one data collection point were examined and compared to those who had completed the emotional well-being measure at all data collection points to assess how the two groups were different and assess any potential impacts (see Tables E-3 and E-4).

2. Missing Data

At baseline, those who had not provided emotional well-being data in at least one data collection point were significantly different than those who had full data the entire study in a number of ways. Children with missing data for emotional well-being were more likely to have quite severe, very severe, or extremely severe

epilepsy (8.0% vs. 5.4%) and were more likely to be identified as having cognitive problems (31.4% vs. 15.7%) compared to children who had complete information. Families whom had missing data for emotional well-being were more often living without a spouse or partner (29.5% vs. 15.3%), more likely to be making less than $40,000 per year (36.1% vs. 17.0%), more likely to have a high school education or less (45.8% vs. 28.7%), were younger (36.2 years vs. 38.2 years), had more depressive symptoms (mean 13.3 vs. 17.0), had less family resources (mean 47.7 vs. 51.0), more family demands (mean 11.1 vs. 8.9), and have less family functioning (13.3 vs. 14.2) compared to families who had complete information.

Families with missing information had lower emotional well-being compared to those with complete data at baseline but this difference was non-significant. Missingness did not predict emotional well-being in univariable analyses as well as in multivariable analyses where potential confounders (child age, education, parental work status, martial status) or family factors (family functioning, family demands, family resources) were added to the model. Results of these analyses can be found in Table E-5.

In growth mixture modeling, estimation of parameters can still occur with partially missing data. In this thesis, Maximum Likelihood (ML) estimation was used where in the presence of missing data, the growth model parameters are estimated based upon the information each individual is able to contribute and the estimator weighs each individual based how much information they provide[1]. An extension of ML, MLR (robust standard errors) can be used with non-normal data and with partially missing data. It is unknown how effective MLR is in handling both missing

and non-normal data, but in our study using both ML and MLR results were consistent. Both estimation methods prioritize full information, such that those who provide full information are weighed more heavily than those who provide less information (due to missing data). For models to be unbiased, missing data is required to be completely missing at random or missing at random (missing data is associated with a measured characteristic)[1]. In our research, data are missing at random.

3. Growth Curve Modeling Diagnostics

Growth curve modeling requires several data distribution assumptions to best ensure non-biased estimate. Those most prominent include independence and multivariate normality.

Intraclass Correlation:

In the data used for this thesis, subjects were recruited from a number of paediatric neurologists or neurology clinics, leading to the possibility that neurologists could include multiple patients from the same location. As such, any clustering effects may bias estimates due to a violation of the assumption of independence if not accounted for in the analysis. The intraclass correlation is a measure of dependence between individuals and can be used to indicate possible clustering effects. Research suggests that if the numbers of individuals within a cluster are small, clustering is only an issue if intraclass correlations are larger than 0.1 and elsewise can be ignored from adjustment[2,3]. In this study, the average number of individual's from a given neurologist and/or clinic was 6 and intraclass correlations were small, suggesting clustering across neurologists to not be an issue.

Due to the repeated measurement occasions from the same individual across time, Growth Mixture Modeling procedures are designed to adjust for the correlated responses within an individual to ensure unbiased estimates.

Multivariate Normality:

The assumption of multivariate normality was examined using probability plots, estimates of skewness and kurtosis, and Mardia's Multivariate Normality Test using only individuals with full data. Results are shown in Table E-6 and Figures E-1 and E-2. Results indicated the data is non-normal, with both skewness and kurosis being significant. The probability plots indicate a small number of individuals in the sample (approximately 5%) have scores that are significantly non-normal. As a result Maximum Likelihood with robust standard errors (MLR) was used to run analyses. The analyses were compared to those obtained using Maximum Likelihood (ML) and both provided identical results, suggesting both ML and trajectory classes were robust to the amount of non-normal data within our sample.

4. Treatment of Outliers

Outliers were examined to assess the influence of an individual on a particular growth trajectory and sample estimates. An individual is considered a statistical outlier when their observation appears at one extreme of the sample's range of values[4]. Outliers were examined based upon their Mahalanobis Distance. In growth curve modeling, a statistical outlier may not be an error but rather natural in that the case is growing at a higher rate or as a result of a dynamic life event leading to unstable growth. This can lead to outliers influencing a growth mixture model by forming their own class. In our study, we identified 20 possible outliers based on

their Mahalanobis Distance (see Table E-7 and Figure E-3). These individuals were approximately evenly spread between the two trajectory classes and did not form a separate trajectory group. While model fit improved when removing these outliers, parameter estimates did not significantly change. As a result, all individuals were kept and are presented in Chapter 6. Based on the dynamic nature of these individuals, it is possible that under a different model, such as a quadratic or cubic shaped trajectory, these individuals may form their own class but we have insufficient sample size and data points to examine this.

References

1. Curran PJ, Obeidat K, Losardo D. Twelve Frequently Asked Questions About Growth Curve Modeling. J Cogn Dev 2010; 11: 121-36.

2. Barcikowski RS. Statistical Power with Group Mean as the Unit of Analysis. J Educ Behav Stat 1981;6:267-85.

3. Kreft I, de Leeuw J. Introducing multilevel modeling. London: Sage Publications; 1998.

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Table E-1. Child Characteristics of the Sample.

		Baseline (n=373)	6 month (n=336)	12 month (n=304)	24 month (n=282)
Age, years	mean (SD)	7.5 (2.3)	7.9 (2.4)	8.5 (2.3)	9.5 (2.3)
Sex	Male	52.4	51.5	50.7	51.6
Epilepsy severity					
Extremely severe		0.3	0.3	0.0	0.3
Very severe		1.1	0.0	0.6	1.0
Quite severe		4.7	3.0	1.5	1.0
Moderately severe		17.0	8.3	6.7	6.0
Somewhat severe		23.6	14.8	12.7	7.6
A little severe		36.0	30.6	32.0	26.6
Not at all severe		17.3	43.0	46.5	57.8
Seizure type					
Partial		59.6	39.2	58.4	57.8
Generalized		38.5	59.0	39.8	39.5
Undetermined		1.9	1.7	1.8	2.7
Frequency of Seizures	mean (SD)	3.3 (1.7)	1.9 (1.3)	1.7 (1.1)	1.6 (1.0)
Current AED use		67.1	81.0	81.8	76.5
Total AEDs Taken	mean (SD)	0.8 (0.7)	1.2 (0.9)	1.3 (1.1)	1.4 (1.3)
Cognitive Problems		20.0	23.0	25.5	28.4
Behaviour Problems		15.4	23.6	20.7	22.7
QOLCE	mean (SD)	72.5	73.8	74.4(13.0)	75.1 (12.9)
Emotional Well-Being		(13.2)	(12.8)		

*Percentages unless noted

Table E-2. Parent Characteristics of the Sample.

	Baseline (n=373)	6 month (n=336)	12 month (n=304)	24 month (n=282)
Marital Status				
Living with a Spouse	87	87	88	88
Other	13	13	12	12
Annual Household Income				
Less than $20,000	8.0	9.5	5.3	3.9
$20,000-$39,999	14.3	13.3	14.5	11.5
$40,000-$59,999	21.4	20.0	18.1	19.2
$60,000-$79,999	19.4	17.5	18.1	20.4
$80,000 or more	37.0	39.7	44.0	45.0
Age- Primary caregiver mean (SD)	37.7 (6.1)	38.2 (5.8)	39.1 (5.9)	40.3 (5.6)
Education – Primary caregiver				
Less than 8 years	1.9	0.6	0.3	0.4
8-12 years	9.4	8.0	6.3	5.3
High school	22.2	21.1	19.7	19.5
Vocational/Technical training	13.1	10.7	13.8	11.4
College/University	44.7	48.8	51.0	51.8
Graduate school	8.8	8.3	8.6	11.7
Employment status – Primary caregiver				
Employed	67.1	70.7	73.5	77.0
Not Employed	32.9	29.3	26.5	23.0
Parental Depression	37.2	25.9	24.9	21.4
Resources, FIRM mean (SD)	50.1 (11.1)	51.0 (11.2)	51.0(11.5)	50.7 (11.5)
Demands, FILE mean (SD)	9.5 (6.5)	N/A	8.0 (6.0)	7.9 (5.7)
Functioning, APGAR mean (SD)	13.9 (3.8)	14.1 (3.7)	13.9 (4.0)	14.1 (3.9)

*Percentages unless noted

Table E-3. Missing vs. Non-Missing Baseline Child Characteristics.

		Non-Missing (n=282)	Missing (n=91)	X^2/ *t*	*p*-value
Age, years	mean (SD)	7.5 (2.3)	7.3 (2.5)	0.76	0.43
Sex	Male	51.1	55.2	0.51	0.4
Epilepsy severity					
Extremely severe		0.4	0.0		
Very severe		0.0	4.0		
Quite severe		5.0	4.0	13.43	**0.04**
Moderately severe		17.9	14.9		
Somewhat severe		21.8	27.7		
A little severe		36.3	35.6		
Not at all severe		18.7	13.9		
Seizure type					
Partial		60.7	56.3		
Generalized		37.8	40.8	1.19	0.55
Undetermined		1.5	2.9		
Frequency of Seizures	mean (SD)	3.2 (1.6)	3.4 (1.7)	-0.60	0.55
Current AED use		64.2	74.5	4.85	0.09
Cognitive Problems		15.7	31.4	11.26	**0.001**
Behaviour Problems		13.5	19.4	2.00	0.16
QOLCE	mean (SD)				
Emotional Well-Being		72.6 (13.5)	71.9 (12.5)	0.50	0.61

*Percentages unless noted

Table E-4 Missing vs. Non-Missing Baseline Parent Characteristics.

	Full Data (n=282)	Missing Data (n=91)	X^2/ *t*	*p*-value
Marital Status				
Living with a Spouse	84.7	70.5	9.8	**0.001**
Other	15.3	29.5		
Annual Household Income				
Less than $20,000	4.7	16.5		
$20,000-$39,999	12.3	19.6		
$40,000-$59,999	22.5	18.6	23.70	**0.001**
$60,000-$79,999	17.8	22.7		
$80,000 or more	42.7	22.7		
Age- Primary caregiver mean (SD)	38.2 (5.6)	36.2 (7.0)	2.73	**0.007**
Education – Primary caregiver				
Less than 8 years	2.2	1.0		
8-12 years	5.6	19.1		
High school	20.9	25.7	19.39	**0.002**
Vocational/Technical training	13.8	11.4		
College/University	48.1	35.2		
Graduate school	9.3	7.6		
Employment status – Primary caregiver				
Employed	68.5	63.1	0.99	0.32
Not Employed	31.5	36.9		
Parental Depression mean (SD)	13.3 (10.2)	17.0 (10.1)	-3.15	**0.002**
Resources, FIRM mean (SD)	51.0 (11.1)	47.7 (10.9)	2.56	**0.01**
Demands, FILE mean (SD)	8.9 (5.8)	11.1 (8.0)	-2.56	**0.01**
Functioning, APGAR mean (SD)	14.2 (3.8)	13.3 (3.5)	2.13	**0.03**

*Percentages unless noted

Table E-5. Univariable and Multivariable Models Examining Prediction of Baseline Emotional Well-Being by Missingness.

	Model 1	Model 2	Model 3
Intercept	72.66 (0.81)	73.06 (3.49)	52.61 (5.58)
Missingness	-0.77 (1.59)	0.02 (1.65)	1.51 (1.54)
Family Functioning (APGAR)	*	*	0.48 (0.21)[a]
Family Demands (FILE)	*	*	-0.24 (0.12)
Family Resources (FIRM)	*	*	0.32 (0.08)[b]

Models 2 and 3 adjusted for living with a spouse, parental education, parent employment status, and child age.
[a]$p<0.05$, [b]$p<0.1$

Table E-6. Assessment of Multivariate Normality.

	Skewness	Kurtosis	Mardia's Multivariate Normality Test
Baseline	-0.90	1.17	$p<0.001$ for both
6-Months	-0.79	0.52	
12-Months	-0.98	0.95	
24-Months	-0.71	0.34	

Results used only those individuals with full information.

Table E-7. Possible Outliers based on their Mahalanobis Distance.

Observation	Mahalanobis Distance
43	49.66
103	41.92
220	27.44
80	22.89
37	22.06
21	21.75
101	21.57
25	19.72
100	17.94
95	15.90
50	14.92
30	14.84
77	14.12
91	13.86
69	13.32
280	13.27
14	13.01
72	12.90
108	11.84
34	11.56

Values larger than 11.143 indicate possible outliers.

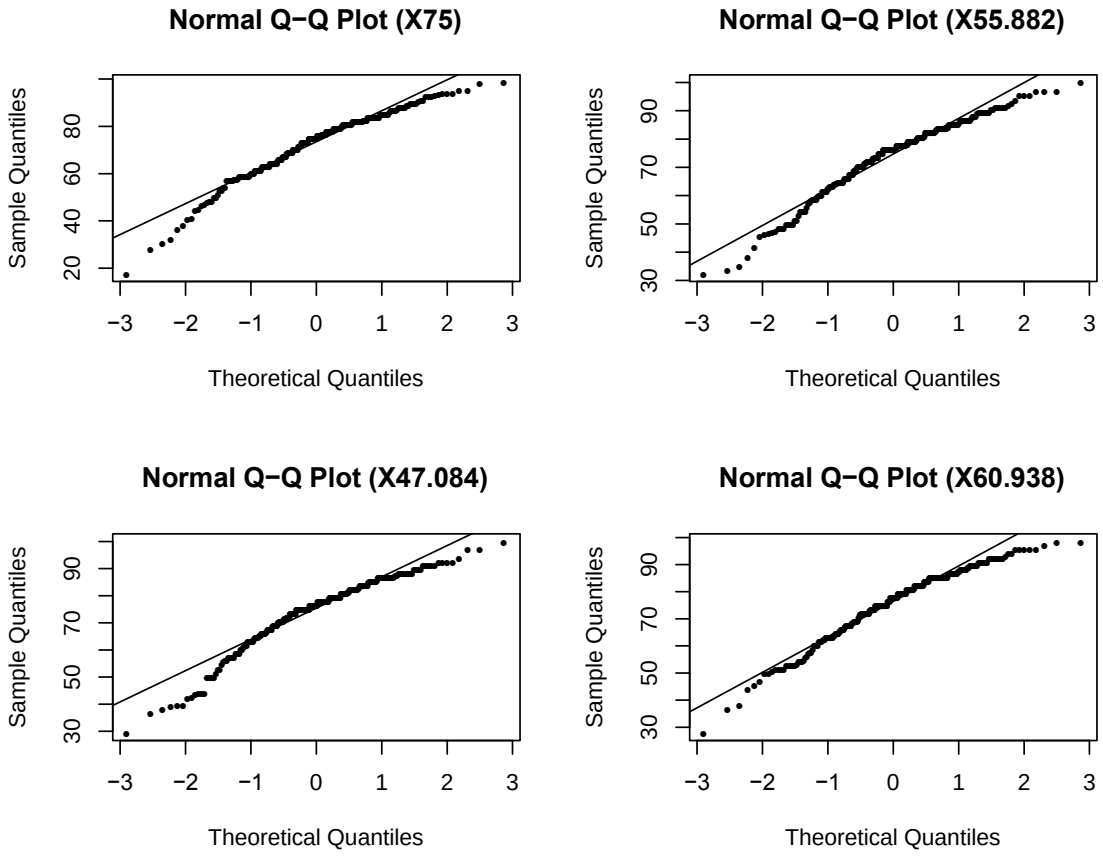

Figure E-1. Probability plots at each time point (Baseline, 6, 12, and 24-Months).

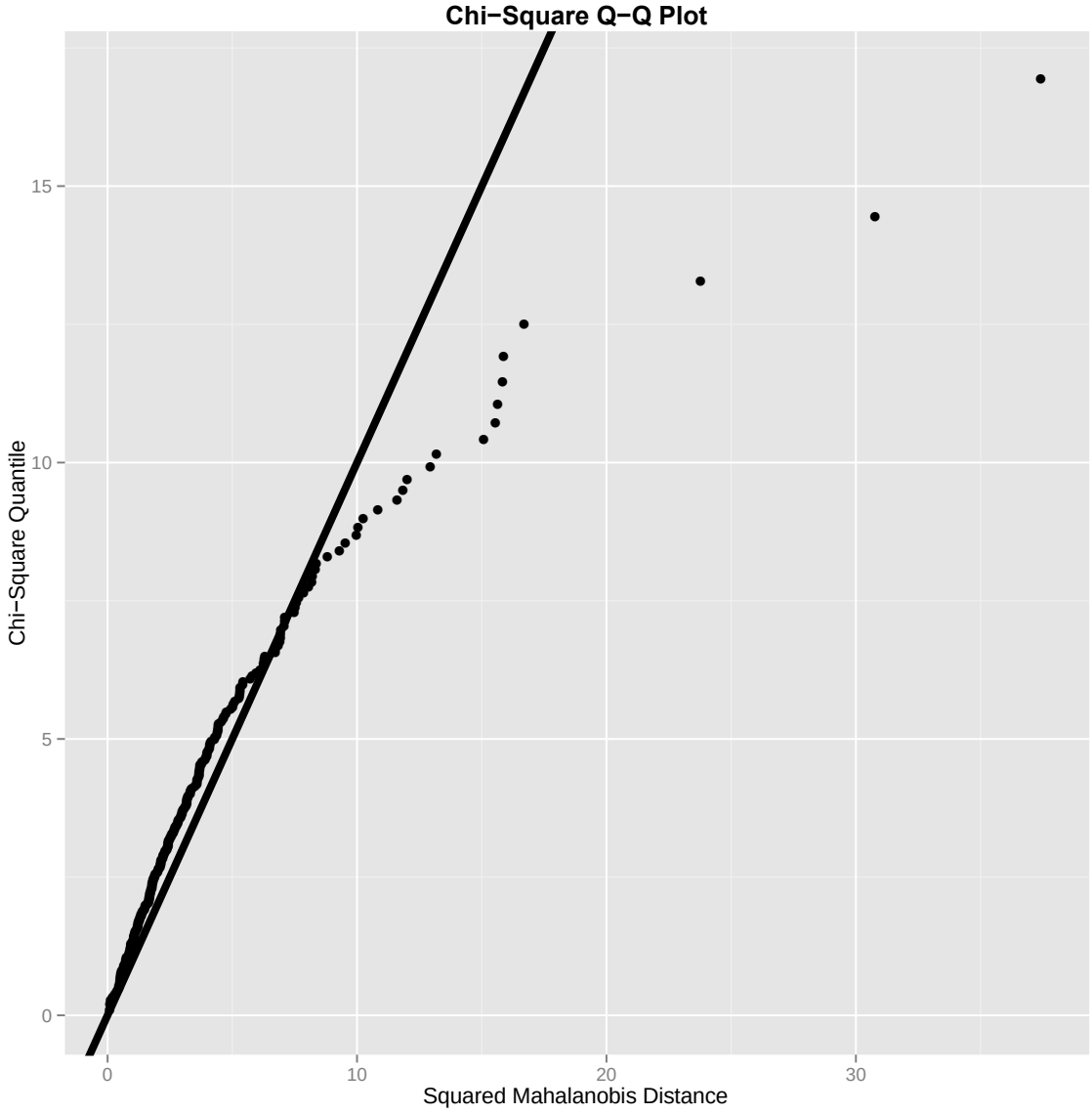

Figure E-2. Mahalanobis Distance Plot to examine multivariate normality.

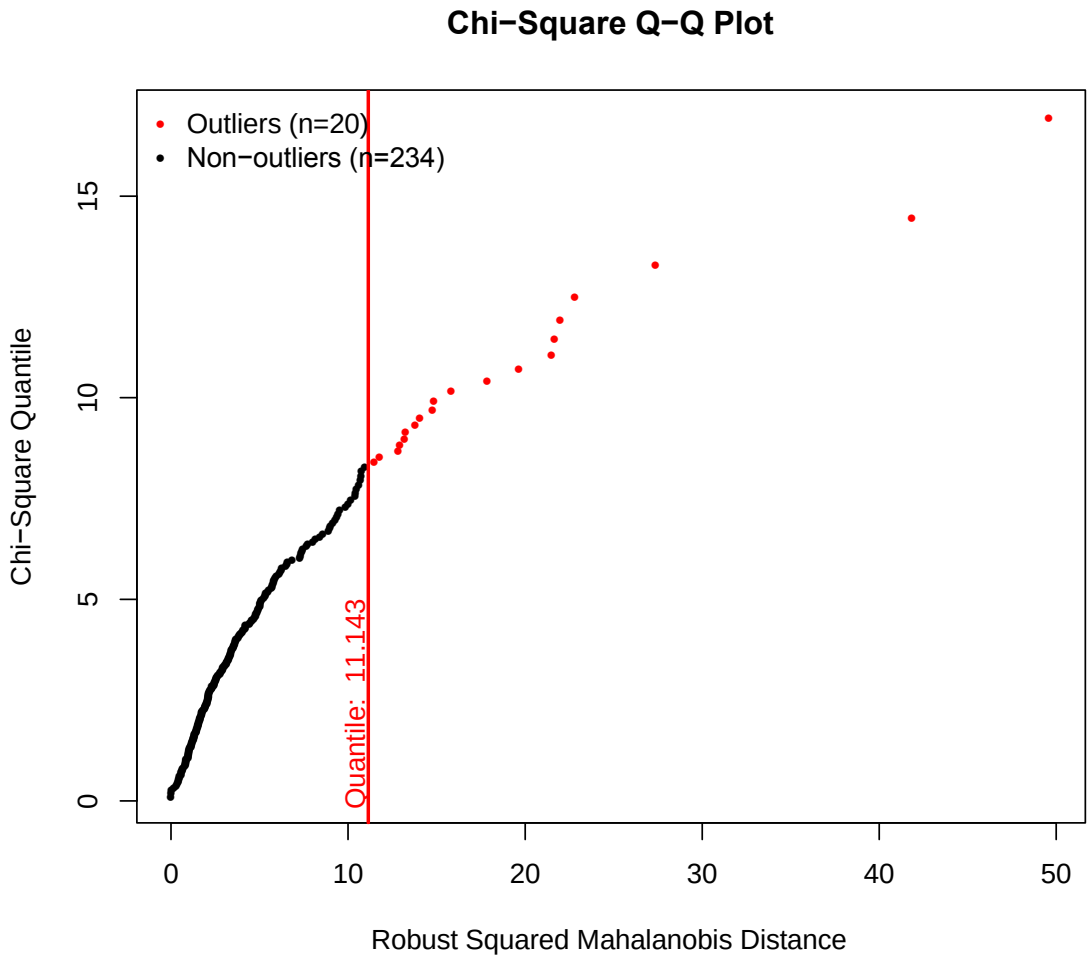

Figure E-3. Probability-Mahalanobis Distance Plot examining possible outliers (individuals with values above 11.143).

Curriculum Vitae

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Goodwin SW, Lambrinos AI, Ferro MA, Sabaz M, Speechley KN. Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). Epilepsia 2015;56: 864-72.