DEPRESSIVE SYMPTOMS IN MOTHERS OF CHILDREN WITH NEW-ONSET EPILEPSY: A PROSPECTIVE STUDY

(Spine Title: Depression in Mothers of Children with New-onset Epilepsy)

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by

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Abstract

Having a child diagnosed with a chronic illness such as epilepsy is a major source of stress for caregivers. Up to half of mothers of children with epilepsy are at increased risk for clinical depression and symptoms of maternal depression are associated with poorer health outcomes in these children. The purpose of this study was to: 1) estimate the prevalence and course of depressive symptoms over 24 months among mothers of children with new-onset epilepsy; 2) identify subgroups of mothers that share similar trajectories of depressive symptoms; and, 3) assess the family factors involved in the causal pathway between maternal depressive symptoms and child health-related quality of life.

The data for this study originated from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES), a national prospective cohort study designed to examine the determinants of health-related quality of life in children with epilepsy during the first 24 months after diagnosis. A total of 339 mothers participated in the study. Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale and health-related quality of life was measured with the Quality of Life in Childhood Epilepsy. Maternal, child, and family factors were measured using valid and reliable measures with a proven track record of use in this population. Multiple regression was utilized to test whether depressive symptoms affected mothers' reports of child outcomes. Latent class growth modeling and multinomial logistic regression were used to identify trajectories of depressive symptoms and predictors of trajectory group membership, respectively. Individual growth curve modeling was used to examine the impact of maternal depressive symptoms on child health-related quality of life, including the moderating and mediating effects of the family environment.

Depressive symptoms were not observed to affect mothers' reports of child health-related quality life in this sample. Four distinct trajectories of depressive symptoms were observed: low stable, borderline, moderate increasing, and high decreasing. A

unique set of predictors was found for membership in each trajectory group. Maternal depressive symptoms were found to have a negative impact on child health-related quality of life during the 24 month follow-up. This relationship was moderated by family resources and the magnitude of moderation varied over time. The relationship between depressive symptoms and health-related quality of life was mediated by family functioning and family demands.

Keywords: child, depression, depressive symptoms, epilepsy, family environment, family-centered care, growth curve modeling, health-related quality of life, longitudinal study, mother, trajectory modeling

Co-authorship Statement

Each of the manuscripts contained within this thesis is based upon research that was primarily conceived of, designed, and analyzed by the author, Mark Anthony Ferro, as a component of his doctoral work. The data for this research were obtained from the Health-related Quality of Life in Childhood Epilepsy Study (HERQULES), the principal investigator of whom was the author's supervisor, Dr. Kathy N. Speechley. Contributions in the form of regular feedback and methodological and statistical advice were provided by each of the co-authors throughout the course of this research study. Mark Anthony Ferro was the primary author of each manuscript; Dr. Kathy Nixon Speechley was co-author of the manuscript associated with Chapter Two of the thesis and Dr. William R. Avison, Dr. Karen M. Campbell, and Dr. Kathy N. Speechley were co-authors of the manuscripts associated with Chapters Three through Five of the thesis, respectively, as indicated in the footnote of the introduction of each of these chapters.

Epigraph

To grow is to change

Blessed John Henry Newman (1801-1890)

Dedication

For Annalise – my colleague, wife, and best friend

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List of Abbreviations

AEDs	anti-epileptic drugs
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterion
CACN	Canadian Association of Child Neurology
CES-D	Center for Epidemiological Studies Depression Scale
CI	confidence interval
CHQ	Child Health Questionnaire
COVRATIO	covariance ratio
Family APGAR	Family Adaptability, Partnership, Growth, Affection, Resolve
FILE	Family Inventory of Life Events and Changes
FIRM	Family Inventory of Resources for Management
GASE	Global Assessment of Severity of Epilepsy
GHQ	General Health Questionnaire
HAD	Hospital Anxiety and Depression Scale
HRQL	health-related quality of life
HERQULES	Health-related Quality of Life in Children with Epilepsy Study
ICC	intraclass correlation coefficient
ILAE	International League Against Epilepsy
MAACL	Multiple Adjective Affect Checklist
MDS	maternal depressive symptoms
MPOC	Measure of Processes of Care
NM	not measured
OR	odds ratio
PPPC	Patient Perception of Patient-centeredness
PSI	Parenting Stress Index
QIS	Quality Index score
QOLCE	Quality of Life in Childhood Epilepsy

SAS	Statistical Analysis Software
SCID	Structured Clinical Interview for DSM-IV
SDS	Self-Rating Depression Scale
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TDM	Tailored Design Method

Chapter One

Introduction and Research Objectives

Background

Estimates of depression are typically derived from depression rating scales designed to measure psychological distress or by clinician interview involving assessment with standardized instruments based upon diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders.[1] Instruments that screen for psychological distress are most often self-report measures used to estimate the levels of depressive symptoms in the general population.[2] In contrast, clinical depression is characterized by a departure from normal functioning and the occurrence of at least five distinct depressive symptoms present during the same two-week period; symptoms must include the presence of a depressed mood and/or loss of interest or pleasure in activities, and may include disturbances in sleep, appetite, energy, motor activity, and concentration, feelings of worthlessness and guilt, and suicidal ideation. While measures of depressive symptoms do not provide a clinical diagnosis of depression, individuals who score above a given threshold are likely at increased risk for clinical depression.[3]

Maternal depression is a universal term encompassing a range of depressive symptoms and syndromes that may affect women during the prenatal period, immediately after childbirth, or later during their child's growth through to adolescence.[4] For women in their reproductive years, the prevalence rate of depression ranges from 8% to 47%, making it the leading cause of disease burden within this population.[5-13] As well, researchers have shown that mothers of disabled or chronically ill children generally experience a higher rate of depression compared to mothers of healthy children. In a recent meta-analysis conducted by Singer, between 6% and 24% more mothers of children with developmental disabilities scored above clinical cutoffs for depression compared to mothers of

children without developmental disabilities.[14] While considerable research has been conducted to understand depression among mothers of developmentally disabled children, very little research has been conducted in other childhood neurological conditions, including epilepsy.

Epilepsy is one of the most common neurological illness affecting children, with an estimated prevalence of 5/1000 children and incidence of 40-50/100,000 children per year in developed countries.[15] Epilepsy is not a single, distinct condition; instead, it is a heterogeneous family of disorders having in common an abnormally increased predisposition to seizures.[16, 17] Recent evidence suggests that many children with epilepsy experience increased rates of psychosocial[18-20] and cognitive[21-23] problems that can reduce their health-related quality of life. As well, children with epilepsy have increased mortality and sudden death compared to healthy children.[24-26] Despite a marked improvement in the treatment of childhood epilepsy with novel therapeutics and surgical techniques, many children never achieve clinical remission[24, 27, 28] and many adverse consequences of childhood epilepsy continue into adulthood.[29-31]

Similar to other childhood chronic illnesses, the impact of epilepsy is not limited to the child experiencing seizures, but affects all members of the family to a certain degree.[32-34] Hoare and Kerley observed that compared to control families, families with a child with epilepsy experienced significantly more stress, anxiety, and restrictions in family life.[33] Thompson and Upton demonstrated that families with a child with epilepsy had increased levels of stress and dissatisfaction with their social situation, decreased levels of marital satisfaction, and low perceived support.[34] In a recent review by Rodenburg et al., families with a child with epilepsy experienced parent-child relationships of lower quality, less competence in parenting, and more problems with family functioning and adaptation compared to control families.[35]

Since mothers are most often the primary caregivers of children,[36] it is reasonable to assume that mothers may experience most of the psychological disturbances in response to their children's epilepsy. Despite results showing some evidence supporting this hypothesis,[37, 38] no one study adequately focuses on parent mental health status, specifically, maternal depressive symptoms in this population. In particular, little is known about the prevalence and predictors of maternal depressive symptoms and how maternal depressive symptoms may impact the health-related quality of life of a child newly-diagnosed with epilepsy and which family factors potentially moderate or mediate this proposed causal relationship. The causal mechanisms underlying intra-family interactions are important in identifying potential targets for intervention in order for paediatric neurology healthcare professionals to provide optimal family-centered care.

Research Objectives

The wide recognition of the impact of a chronically ill child on the family, especially the mother, challenges paediatric healthcare professionals to develop better family-centered care. Within this context, the aims of this research were to prospectively estimate the prevalence and course of depressive symptoms among mothers of children with newly-diagnosed epilepsy seen by a paediatric neurologist across Canada, identify predictors of maternal depressive symptoms, and assess the causal mechanisms that describe the impact of maternal depressive symptoms on the health-related quality of life of children with epilepsy. Specific objectives for the proposed study were to:

1. Estimate the prevalence and course of depressive symptoms over 24 months among mothers of children with new-onset epilepsy.
    a. What is the prevalence of elevated depressive symptoms among mothers at baseline, and 6, 12, and 24 months after the child's diagnosis of epilepsy?
    b. How do depressive symptom trajectories change over time?

2. Identify subgroups of mothers that share similar trajectories of depressive symptoms and assess maternal, child, and family factors associated with group membership.
    a. What subgroups of mothers share trajectories of depressive symptoms?
    b. What maternal, child, and family factors predict depressive symptom trajectory group membership?

3. Assess the family factors involved in the causal pathway between maternal depressive symptoms and child health-related quality of life over 24 months and the extent to which family factors moderate or mediate this relationship.
    a. Do changes in maternal depressive symptoms predict changes in child health-related quality of life?
    b. Do family resources moderate the relationship between maternal depressive symptoms and child health-related quality of life?
    c. Does perception of patient-centered care moderate the relationship between maternal depressive symptoms and child health-related quality of life?
    d. Does family functioning mediate the relationship between maternal depressive symptoms and child health-related quality of life?
    e. Do family demands mediate the relationship between maternal depressive symptoms and child health-related quality of life?

Prior to examining the specific research objectives for this study, a methodological issue central to the analyses was identified. Given that much of the data collected in the study was obtained via maternal reports, an investigation to determine whether mothers of children with new-onset epilepsy exhibiting depressive symptoms provide accurate reports of child outcomes was conducted. The specific question asked was, “Do depressive symptoms moderate the relationship between mothers’ and neurologists’ reports of children’s health-related quality of life?”

Conceptual Framework

The theoretical framework used to guide this research was adapted from Pearlin's stress process model and is illustrated in Figure 1.1.[39, 40] This framework is rooted in both social stress theory and empirical findings from the medical sociology literature.[40, 41] It has a strong track record of use in epidemiologic research and has been used in an variety of studies examining psychological disturbances in several populations.[42-46] As stated by Turner and Lloyd, the stress process identifies and specifies the inter-relationships among experiences and social and personal resources hypothesized as relevant to a health outcome.[46] It is through these relationships that researchers are able to elucidate the causal mechanisms between a specific stressor and outcome and identify potential targets for intervention so as to negate the negative effect a stressor may have on an individual's health. According to this particular model, the stress process consists of primary stressors (i.e., diagnosis of childhood epilepsy, living with childhood epilepsy), secondary stressor (i.e., maternal depressive symptoms), stress mediators (i.e., family demands and functioning), stress moderators (i.e., family resources, perception of patient-centered care), a stress outcome (i.e., child health-related quality of life), and various potential confounders (e.g., child and maternal age, marital status, socioeconomic status, etc.) influencing the process.

Stressors can appear in two common forms: life events and chronic strains. Life events are classified as having a discrete, identifiable point in time at which it occurred (e.g., diagnosis of childhood epilepsy), whereas chronic stressors are more likely to emerge insidiously and be persistent (e.g., living with epilepsy). Pearlin et al. note that life events and chronic strains may produce stress in two ways.[39] First, the experience of stressful life events may alter meanings of existing strains; second, life events may generate new or magnify existing strains. The initial stressor is considered the primary stressor and those that follow as secondary. The terms "primary" and "secondary" do not imply that one is more influential on outcomes; instead, the terms are used to distinguish the temporal order in which the stressors

are observed.[40] Therefore, the model presumes that stressors do not arise simultaneously in individuals' lives, but appear sequentially as the process unfolds, therefore clarifying the causal mechanisms between exposure and outcome.[47] Evidence for the meditational role of family factors between maternal depressive symptoms and child outcomes have been demonstrated in a number of longitudinal studies.[48-52] Recently, Cummings et al. studied a community sample of 235 parents of kindergarten children and observed that family stressors and functioning, specifically, marital conflict, significantly mediated the relationship between parental depressive symptoms and child psychosocial outcomes.[53]

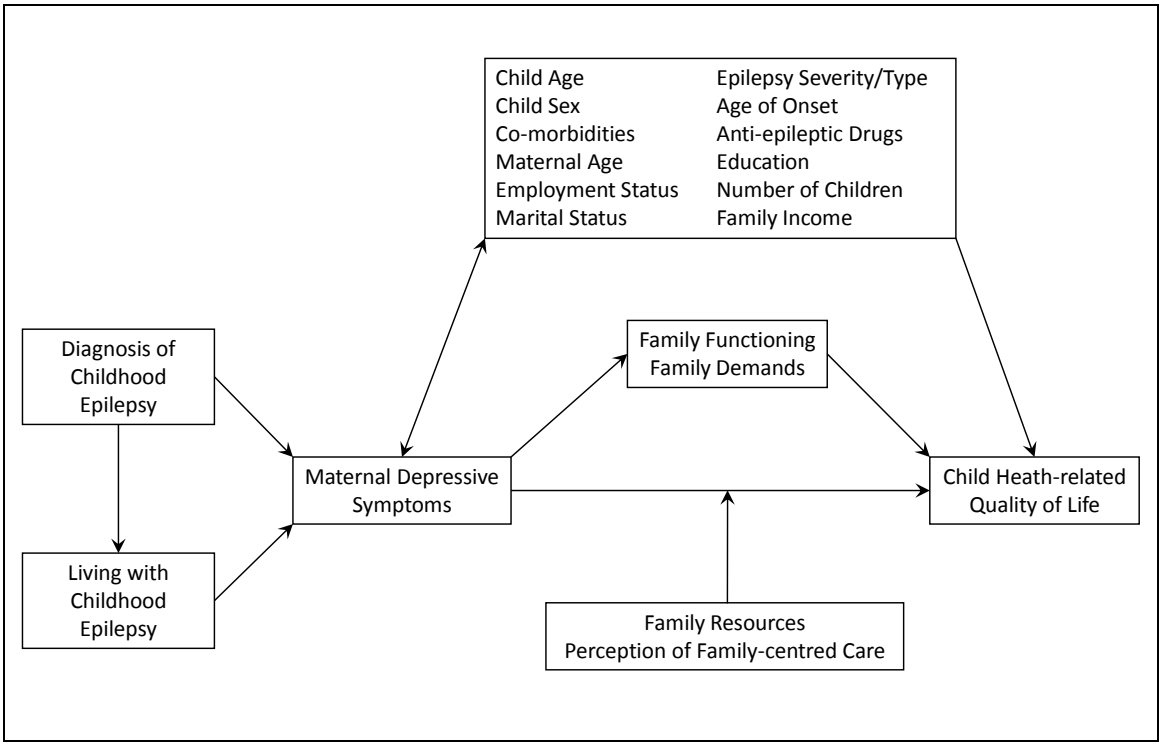

Figure 1.1. Conceptual Framework based on a Stress Process Model.

In addition to hypothesizing the existence of mediating effects between maternal depressive symptoms and child health-related quality of life, the model also permits the inclusion of hypothesized moderating effects that can exert their effects on various pathways within the process. The examination of these relationships increases the complexity of the model, but provides richer, more accurate data for understanding this particular stress process.[41] Moderators of this relationship have

been identified and include, family factors, such as resources, as well as child characteristics including, gender and age. In their review, Elgar et al. discussed the evidence supporting family resources as a moderator in the relationship between maternal depression and child adjustment problems, whereby greater resources buffer the negative effects of maternal depression.[54] Other researchers have highlighted gender-[51, 52, 55] and age-specific pathways.[48, 56] In a study of 69 mother-child dyads, Carter et al. showed that maternal depressive symptoms predicted behaviour problems in male, but not female children.[57] Ghodsian et al. observed that the negative impact of maternal depression on child behaviour problems were significant for older children only.[58] Stress mediators and moderators represent components along the causal pathway that may be amenable to interventions that mute the potential negative influence maternal depressive symptoms may have on the health-related quality of life of children.

The stress outcome, in this case, child health-related quality of life represents the converging consequences of all other components in the model. The impact of maternal depressive symptoms on child health-related quality of life is a reasonable hypothesis considering the fact that stressors experienced by one family member most often induce stress in other members of the family.[39-41] Evidence supporting this hypothesis has been demonstrated in several longitudinal examinations of maternal depressive symptoms and child behaviour problems.[55, 58-66] In each of these studies, symptoms of depression in mothers preceded subsequent child behaviour problems including, defiance, aggression, and hyperactivity. Potential confounders are included in the stress process in order to obtain unbiased measures of effect among components of the model.

Structure of the Thesis Document

In accordance with The University of Western Ontario's School of Graduate and Postdoctoral Studies' guidelines, the work of this thesis will be presented in a series of four manuscripts. A brief description of these manuscripts is provided below. A

complete description of the methodological details of this thesis is provided in several appendices at the end of this document (Appendices A, C, and E). Additional appendices are provided for statements of ethics approval (Appendix B), survey instruments (Appendix D), and additional information and analyses for the thesis (Appendices F through J).

The literature review is presented in Chapter Two. A version of this chapter was published entitled, "Depressive symptoms among mothers of children with epilepsy: a review of prevalence, associated factors, and impact on children" in Epilepsia in 2009. This paper contains a review of the literature with an evaluation of the studies' results within the context of their methodological strengths and weaknesses.

Chapter Three includes a manuscript entitled "Do depressive symptoms affect mothers' reports of child outcomes in children with new-onset epilepsy?" was published in 2010 in Quality of Life Research. Given that mothers were the primary informant for this research, this manuscript was developed to examine the methodological issue of whether depressive symptoms distort mothers' reports of child outcomes.

Chapter Four includes a manuscript entitled "Prevalence and trajectories of depressive symptoms in mothers of children newly-diagnosed with epilepsy" was published in 2011 in the journal Epilepsia. The purpose of this manuscript was to address the first and second objectives of this thesis.

Chapter Five includes a manuscript entitled "The impact of maternal depressive symptoms on health-related quality of life in children with epilepsy: a prospective study of family environment as mediators and moderators" was published in 2011 in Epilepsia. The purpose of this manuscript was to address the third objective of this thesis.

The final chapter, Discussion: Summary and Conclusions (Chapter Six), summarizes the main findings of this dissertation and relates each of the chapters to one another, as well discusses the implications for future research. A broader discussion of the strengths and limitations of the study is included in this chapter.

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Chapter Two

Literature Review[a]

Background

Research thus far has demonstrated that childhood epilepsy affects families in terms of its psychosocial consequences. Since mothers are most often the primary caregivers of children,[1] it is reasonable to assume that mothers may be particularly at risk for distress in response to their children's epilepsy, most notably depression.[2, 3] Thus, it is important to critically evaluate the available evidence regarding the prevalence of elevated levels of depressive symptoms among mothers of children with epilepsy, correlates of maternal depressive symptoms, and the impact of maternal depressive symptoms on child outcomes.

Methodology

A literature search of published studies was conducted in February 2009. The electronic databases MEDLINE and EMBASE were searched simultaneously via the OVID system using the following keywords: 1) adolescent OR child; 2) mother; 3) epilepsy OR childhood epilepsy; 4) depression OR depressive symptoms OR psychological distress; 5) maternal depression OR maternal depressive symptoms OR maternal psychological distress; 6) #1 AND #3; 7) #2 OR #4; 8) #5 OR #7; 9) #6 AND #8. All Medical Subject Heading (MeSH) terms were exploded in order to broaden the search for relevant studies. In addition, the ancestry method of reviewing the references of empirical studies and reviews for other relevant articles not identified with the initial search strategy was used to identify further studies reporting on maternal depressive symptoms in childhood epilepsy. As well, the Web

[a]A version of this section was published elsewhere as, Ferro MA, Speechley KN. Depressive symptoms among mothers of children with epilepsy: a review of prevalence, associated factors, and impact on children. Epilepsia 2009;50(11):2344-354.

of Science electronic database was used to identify newer publications that cited studies already retrieved. The result of each stage of the search methodology employed in this review is illustrated in Figure 2.1.

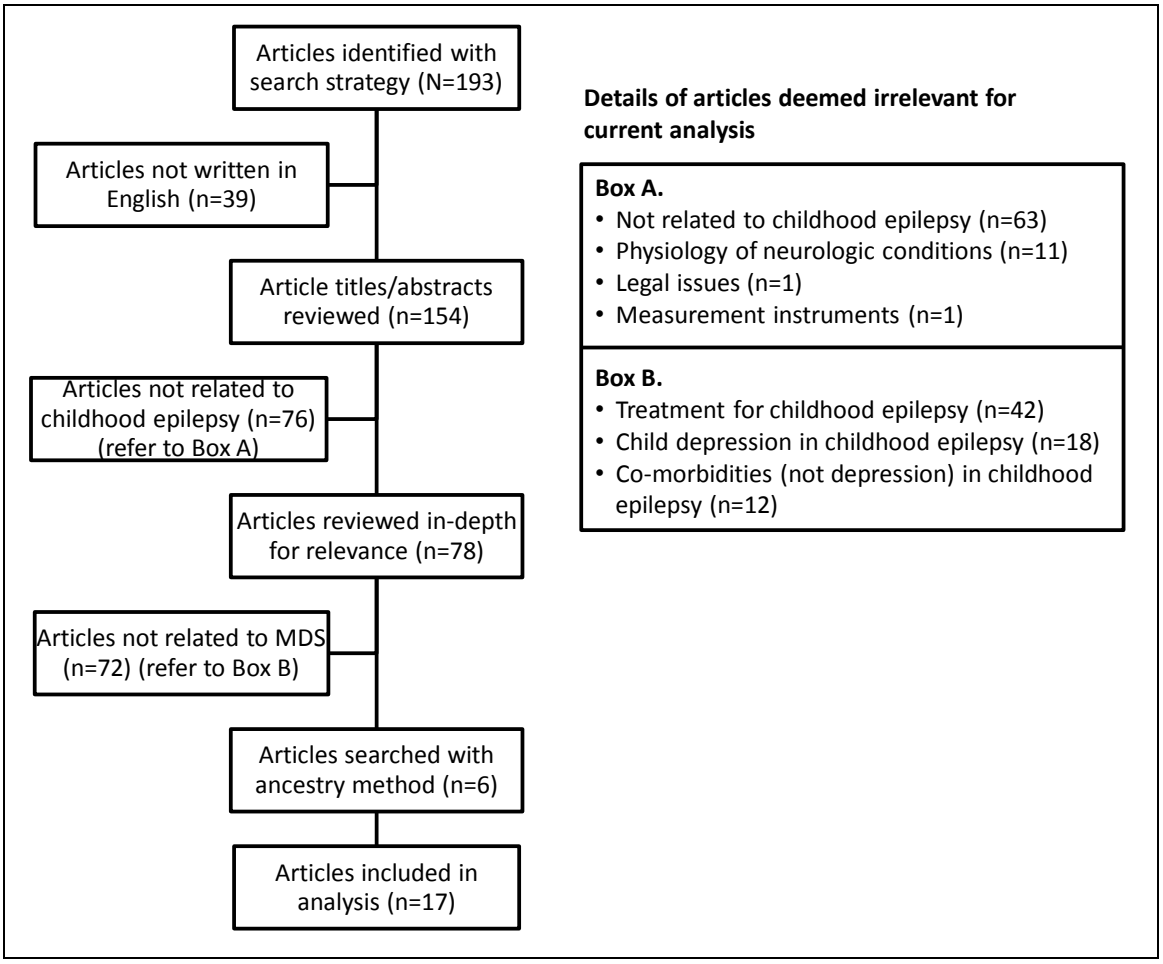

Figure 2.1. Search Process Utilized and Outcomes Obtained in Identifying Articles for the Review. MDS, maternal depressive symptoms.

To meet the criteria for inclusion in this review, a study needed to: 1) report on prevalence of maternal depressive symptoms and/or the relationship between maternal depressive symptoms and child outcomes in families of a child with epilepsy; 2) include families of a child with epilepsy up to 18 years of age; and, 3) be written in English. Studies included mothers of children with various epileptic seizure and syndrome types and children with or without other conditions, such as cognitive disability.

Retrieved articles underwent quality assessment utilizing a modified version of the Quality Index.[4] While initially developed to systematically rate the research quality of both randomized and non-randomized studies of healthcare interventions to aid with evidence-based medical decision-making, it has been shown to be valid and reliable for measuring the methodological quality of epidemiologic and health research.[4-9] For the purposes of this review, the original 27-item Quality Index was modified to exclude assessment of items related specifically to intervention studies, including randomization, blinding, withdrawals and drop-outs, and intervention integrity, reducing it to 15 items as shown in Table 2.1. Each checklist item was scored 0 (no/unable to determine) or 1 (yes), with a maximum score of 15. Three subscales comprised the Quality Index: reporting (0-7), external validity (0-3), and internal validity (0-4). Study power was assessed with a single item (0-1). Higher scores indicated studies of higher methodological quality.

The 15 studies reviewed here reflect research conducted over a 24-year period from 1984 to 2008. The results reflect a global perspective with three studies conducted in both the United States and Taiwan, two in the United Kingdom, Nigeria, and Turkey, and one each in Canada, China, and the Netherlands. Eight measures were used to assess maternal depressive symptoms in the studies reviewed. These were the Beck Depression Inventory (BDI),[10] Center for Epidemiological Studies Depression Scale (CES-D),[11] General Health Questionnaire (GHQ),[12] Hospital Anxiety and Depression Scale (HAD),[13] Multiple Adjective Affect Checklist – Depression Subscale (MAACL-DS),[14] Parenting Stress Index (PSI),[15] Structured Clinical Interview for DSM-IV (SCID),[16] and Self-Rating Depression Scale (SDS).[17]

Study Quality

The mean total score on the modified Quality Index was 9.7 (standard deviation 1.7), with scores ranging between 7 and 13. The mean subscale scores were 6.0 (0.9), range 4-7 for reporting, 0.6 (0.8), range 0-2 for external validity, and 3.1 (0.4), range 3-4 for internal validity. No study reported a formal sample size or power

calculation. Table 2.2 summarizes the key features of each study reviewed. Of the 15 studies, seven studies assessed the prevalence of maternal depressive symptoms,[18-24] five examined correlates for depressive symptoms in mothers,[23-27] and nine investigated the impact of maternal depressive symptoms on child outcomes in childhood epilepsy.[18, 20, 22, 24, 28-32] There were no significant differences between study types with respect to scores on the overall Quality Index ($F_{2,14}$=1.14, p=0.3510) or subscales for reporting ($F_{2,14}$=0.23, p=0.7951), external validity ($F_{2,14}$=0.98, p=0.4028), and internal validity ($F_{2,14}$=2.67, p=0.1101). Scores were proportionately lower for the external validity subscale as compared to the reporting and internal validity subscales.

Prevalence of Maternal Depressive Symptoms

The mean Quality Index score for studies assessing prevalence of maternal depressive symptoms was 10.6 (1.8). For the reporting, external validity, and interval validity subscales, the mean scores were 6.2 (0.8), 1.0 (1.0), and 3.4 (0.5), respectively. Six studies reported between 12% and 49% of mothers caring for children with epilepsy either met or scored above the clinical cutoffs for depression based on a self-report screening measure.[18-20, 22, 24, 27] One study by Iseri et al., measured clinical depression and found that 32% of mothers of children with epilepsy had a major depressive disorder.[21]

There is a lack of consistency in results of studies comparing rates of depressive symptoms in mothers of children with epilepsy and the general population. In a sample of 115 mothers of adolescents with epilepsy, researchers observed that the mean score on the CES-D was significantly higher than that of a national sample in the United States (14.5 vs. 8.7, p<0.0001), indicating higher levels of depressive symptoms among mothers of children with epilepsy.[20] In contrast, Baki et al., observed that the difference in proportion of mothers classified as depressed according to the BDI was not significantly different between Turkish mothers of children with epilepsy compared to mothers of children without epilepsy (49% vs.

41%, $p>0.05$).[18] In the only study comparing parents of children with epilepsy and another chronic illness, Chiou and Hseih observed similar rates of depression between parents of children with epilepsy and asthma.[19] Using parent-report on the depression subscale of the Parenting Stress Index, 16.3% of children with epilepsy and 18.5% with asthma from a sample of children 8-13 years old attending a hospital clinic in Taiwan scored above the threshold for increased risk of depression (i.e., at or above the 90th percentile). The difference was not statistically significant ($p=0.0861$).

Factors Associated with Maternal Depressive Symptoms

The mean Quality Index score was 9.0 (0.8) with subscale scores of 5.8 (0.5), 0.3 (0.5), and 3.0 (0.0) for reporting and external and internal validity, respectively. The earliest work conducted by Mu et al., investigated correlates of maternal depressive symptoms among a sample of 324 mothers of children with epilepsy attending epilepsy day-clinics at teaching hospitals in Taiwan.[26] Using the BDI, level of maternal depressive symptoms was positively associated with role ambiguity and the worry associated with childhood epilepsy and negatively associated with maternal age. Mu et al., replicated this study in another sample of 316 mothers. Results provided further support for the association between role ambiguity and worry with maternal depressive symptoms.[25] In addition, this subsequent study showed that depressive symptoms were associated with the presence of co-morbidities in the child with epilepsy and lower maternal education.

Further research in this area was conducted by Shore et al.[23, 27] In their initial study of 115 mothers of adolescents with epilepsy, Shore et al., utilized the CES-D to determine the factors associated with level of maternal depressive symptoms.[23] Results demonstrated that adolescent behaviour problems had a significant positive association with maternal depressive symptoms, whereas family income and satisfaction with family relationships had a significant negative association with maternal depressive symptoms.

The results from a recent study by Wood et al.,[24] failed to replicate the findings of maternal and family correlates for maternal depressive symptoms demonstrated by Mu et al.,[25, 26] and Shore et al.[23, 27] Wood et al., found that the only factor associated with maternal depressive symptoms was the presence of behaviour problems, specifically, attention deficit hyperactivity disorder in the child with epilepsy (β=0.49; p<0.004).[24] However, the absence of significant associations between maternal and family factors and depressive symptoms might be attributed to lack of statistical power due to the small sample size studied, rather than a true absence of correlation.

Impact of Maternal Depressive Symptoms on Child Outcomes

Maternal depressive symptoms have been linked to a host of child health outcomes. Most commonly, children of mothers with depression are at a significantly higher risk for internalizing and externalizing behaviour problems[33-37] and depression[38-42] as compared to children of mothers without depression. As well, research has demonstrated that mothers with depression have poorer interactions with their children leading to deficiencies in the overall care of their children.[43-45] In childhood epilepsy specifically, several studies have been conducted describing family factors that are associated with child outcomes, most commonly behaviour problems.[46-56] Nine studies have specifically focused on the impact of maternal depressive symptoms. These studies had a mean Quality Index score of 9.5 (1.9) and subscale scores of 6.0 (1.3) for reporting, 0.5 (0.8) for external validity, and 3.0 (0.0) for internal validity.

Although Dunn and Austin suggest that a family history of depression is an important clue in diagnosing depression in children with epilepsy,[57] Baki et al., showed that there was no correlation between level of maternal depressive symptoms and depression scores in children with epilepsy.[18] This result was also observed by Dunn et al.[20] This contrasts the data analyzed by Adewuya and Ola demonstrating that presence of psychiatric morbidity in parents as measured by the

GHQ was significantly associated with either an anxiety (p=0.021) or depressive (p=0.001) disorder in adolescents with epilepsy.[29] This verified earlier work by Hoare and Hoare and Kerley showing that past and current treatment for psychiatric disturbances in the mothers of children with epilepsy was associated with psychiatric disturbances in children.[30, 31] In addition, Hoare observed that GHQ scores in mothers of children with psychiatric disturbances were greater than in mothers without disturbed children (p=0.04).[30]

Two studies have examined the impact of depressive symptoms on behaviour problems in children with epilepsy. In a sample of 91 parents (81 mothers) of children with epilepsy from a tertiary epilepsy care center in the Netherlands, Rodenburg et al., demonstrated that parental depressive symptoms were significantly correlated with both internalizing (r=0.33, p<0.01) and externalizing behaviour problems (r=0.32, p<0.01).[22] In this study, feelings of depression were measured with the SDS. The data also showed that the impact of parental depressive symptoms on internalizing problems was mediated by parental rejection of the child and that relationship quality with the child mediated the association between parental depressive symptoms and externalizing problems. Yong et al. studied a sample of 418 parents of children with epilepsy at a tertiary care center in China using the HAD to measure parents' level of depressive symptoms.[32] Multivariable regression showed that parental depressive symptoms were significantly associated with child behaviour problems while controlling for the effects of child mental development, maternal age, and duration of epilepsy (p=0.04). However, parental depressive symptoms explained only 5% of the total variance in child behaviour problems.

Three studies have assessed the impact of maternal depressive symptoms on child health-related quality of life revealing some support for a negative impact of maternal depressive symptoms on overall health-related quality of life in children with epilepsy. In a study by Adewuya conducted in Nigeria of 86 adolescents with epilepsy recruited from neuropsychiatric outpatient clinics, maternal depressive

symptoms as measured by the SDS, were significantly associated with child health-related quality of life.[28] This strong negative association (r=-0.66, p<0.001) remained after controlling for the effects of number of anti-epileptic drugs, side effects of treatment, duration of epilepsy, and maternal psychopathology (β=-0.29, p=0.001). Yong et al., also investigated this relationship and showed a significant negative association between parental depression and child health-related quality of life (r=-0.41, p<0.001); however, this association was negated in a multivariable analysis controlling for number of anti-epileptic drugs, seizure frequency, parental anxiety, and family socioeconomic status.[32] Wood et al., performed a zero-order correlation analysis and showed that maternal depressive symptoms were negatively associated with child health-related quality of life, as measured with the Impact of Pediatric Epilepsy scale, whereby higher scores indicate worse quality of life (r=0.51, p<0.0001).[24]

Discussion

This review suggests that a relatively high proportion of mothers of children with epilepsy exhibit depressive symptoms. However, due to the predominance of cross-sectional studies in the field, it remains to be understood what the trajectory of maternal depressive symptoms is over time. Specifically, it is unknown whether depressive symptoms in mothers increase, decrease, or remain stable during the course of childhood epilepsy. In addition, previous studies have primarily examined mothers of children with prevalent cases of epilepsy, which cannot establish when during the illness process symptoms of depression began. Such gaps in the literature suggest the value of developing prospective studies that focus on incident cases of childhood epilepsy and examine changes in maternal depressive symptoms over time.

Furthermore, evidence suggests a role for maternal, child, and family risk factors for depressive symptoms in mothers of children with epilepsy, many of which are amenable to intervention, including family functioning and support. However,

results from previous cross-sectional studies simply identify *correlates*, and not *predictors* of maternal depressive symptoms. True predictors can only be identified with prospective research that includes at a minimum, two measurement occasions. It is with prospective studies that researchers may identify true risk factors and develop interventions designed to decrease the risk of mothers developing depressive symptoms.

Available evidence suggests a significant negative relationship between maternal depressive symptoms and child outcomes in epilepsy. However, no prospective studies were found to verify whether these relationships are in fact causal in childhood epilepsy. Broadening the search to prospective studies in other mother-child populations demonstrates that depressive symptoms in mothers negatively impact child outcomes including child adjustment and behaviour.[58-60] It remains to be seen whether results can be replicated with prospective studies in childhood epilepsy and expanded to include other important child outcomes, including clinical outcomes and health-related quality of life. In addition, moderation and mediation analyses that help to elucidate the causal mechanisms whereby maternal depressive symptoms influence child outcomes are needed. Such studies would be valuable in identifying potential targets for intervention so as to negate the effects of depressive symptoms on child outcomes in epilepsy.

The studies conducted thus far provide preliminary, albeit important contributions to understanding the prevalence, correlates, and impact of maternal depressive symptoms in the context of epilepsy in childhood. With this important groundwork completed, future research should build upon these initial studies to further the knowledge base. Development of robust study designs and methods requires an assessment of the limitations of available literature in order to advance this research agenda. These limitations, which can be grouped in terms of study design, external validity, and internal validity, are discussed in the following section.

Study Design

All studies reviewed used cross-sectional designs. While they represent an important initial step in identifying correlates of maternal depressive symptoms, they are limited to correlation inferences. Causation cannot be inferred from these studies since temporal order of cause and effect is a necessary criterion for causation.[61] For example, in the studies by Adewuya and Yong et al., it is not possible to conclude that maternal depressive symptoms caused a decline in child health-related quality of life.[28, 32] It is equally plausible that a child exhibiting worse health-related quality of life led to depressive symptoms in his or her mother. Implementing prospective cohort studies will clarify the temporal order of cause and effect and allow for the rigorous examination of various causal mechanisms, including factors that predict maternal depressive symptoms and the impact maternal depressive symptoms have on child outcomes in epilepsy over time. Identification of mediating effects along these causal pathways could inform the planning of individualized family-centered care strategies for families of children with epilepsy. In addition, prospective cohort studies make it possible to track rates of elevated depressive symptoms in mothers over the course of their child's illness, which in turn may help healthcare professionals prevent the onset of clinical depression in these women.

External Validity

Since the majority of studies were conducted at a single clinic at a tertiary care center and imply use of non-probability convenience sampling for participants, it is difficult to determine if the samples studied adequately represent the target population. A mean of 0.6 out of a maximum score of 3.0 on the external validity subscale of the Quality Index suggests a need for caution in generalizing results from the studies reviewed. Few studies explicitly reported using convenience sampling[20, 25] and only one study used a combination of random and convenience sampling; however, details of the random sampling procedure were not described.[19] Using

hospital-based convenience samples of families attending outpatient clinics at tertiary care centers compromises the external validity of results since these samples may exclude families whose children's epilepsy is well-controlled by either a paediatrician or other healthcare professional. Thompson and Oxley observed that children recruited from hospital outpatient clinics are more likely to over-estimate severe cases of epilepsy and as a result, researchers should provide comparative measures of childhood epilepsy between the sample and population.[62] It is reasonable to infer that mothers of children with more severe illness may be at greater risk for clinical depression and thus results from these studies may over-estimate the prevalence of elevated levels of depressive symptoms in this population of mothers. It is also possible that the studies reviewed have an over-representation of families who are compliant with the care prescribed for their children, since they were recruited during their scheduled medical appointment. This may also lead to an over-estimate of mothers with elevated depressive symptoms. Research has demonstrated that mothers exhibiting elevated depressive symptoms utilize more healthcare services, including visits to healthcare professionals compared to mothers who do not exhibit depressive symptoms.[63]

Population-based, random sampling procedures provide an efficient strategy to prevent selection bias since mothers across the epilepsy severity spectrum will be more adequately represented. Results pertaining to the prevalence and correlates of maternal depressive symptoms obtained with population-based strategies will provide stronger evidence to support potential changes to public health policy, as well as help implement more appropriate family-centered care. However, there are feasibility constraints in designing population-based studies. In the absence of population-based registries for epilepsy to facilitate such studies, Speechley et al., demonstrated that it may be feasible to recruit a representative population-based sample of children with epilepsy by targeting paediatric neurologists.[64] In this study, family physicians practicing in southwestern Ontario, reported they would refer between 80-99% of their patients with childhood epilepsy (depending on the type of seizure and syndrome) to a paediatric neurologist. The specific geographical

jurisdiction for this study may limit extrapolation to other areas in Canada and abroad, however.

Research has shown that a large proportion of children with epilepsy have other co-morbid conditions, particularly cognitive disability and other neurological problems.[65, 66] For example, in a recent study by Hoie et al., 35% of children with epilepsy had severe, non-verbal cognitive problems.[67] However, only six studies reviewed included children with cognitive disabilities or other co-morbidities.[22, 24-27, 32] Excluding children with epilepsy who have co-morbidities from studies avoids the methodological challenges of dealing with heterogeneous samples. It also means, however, that results are unlikely to reflect the realities faced by this large subgroup, especially in analyses that aim to quantify the impact of epilepsy on the family. By recruiting more representative samples, these studies may provide more accurate estimates that can be more readily applied in the paediatric neurology setting.

Internal Validity

Due to the potential for bias in most observational studies, adequate control of confounding variables is paramount to producing internally valid results when assessing causative relationships. A mean score of 3.1 out of a possible 4.0 on the internal validity subscale of the Quality Index suggests that the studies reviewed were adequate in generating internally valid results, but there still exists room for improvement. Studies conducted by Adewuya and Yong et al., controlled for confounding effects using multivariable regression analyses and are an improvement over simple unadjusted bivariable correlations.[28, 32] Although these studies do provide adjusted estimates of the impact of maternal depressive symptoms on child health outcomes, the use of automated modeling techniques may result in the exclusion of some important confounders, biasing the effect estimates. Modeling causal relationships between maternal depressive symptoms and child

outcomes should focus on a model building process that is researcher-driven and accounts for confounders as determined by theory and empirical evidence.

In addition to confounding, measurement errors can also invalidate results. Due to the challenging nature of surveying children,[68] the use of mothers as a proxy reporter has become standard in child and family health research despite its inherent limitations.[69] Using only proxy measures fails to capture the fact that mothers and children with epilepsy may differ in their perception of health.[70] Other viable options to lessen the impact of information bias may include parallel reports, whereby both mothers and children are asked to report on outcomes. As well, for certain outcomes (e.g., behaviour), persons external to the family may be recruited (e.g., teacher-report of behaviour). Although mothers may have a better understanding of the health issues being examined and the content of questionnaires compared to children, the young patient's experience with illness should also be acknowledged in future investigations.

Conclusion

Taken together, the results from the preliminary studies reviewed demonstrated that a significant proportion of mothers caring for children with epilepsy have elevated levels of depressive symptoms; many correlates of maternal depressive symptoms are potentially modifiable; and, maternal depressive symptoms have a significant negative association with health outcomes in children with epilepsy. This means that a large proportion of children may potentially experience less than optimal outcomes as a result of the consequences of having a depressed mother. Results from the current literature indicate that many predictors of maternal depressive symptoms, as well as mediating factors that impact child outcomes in epilepsy are modifiable. The fact that the studies reviewed had a mean Quality Index at approximately the midpoint of the scoring instrument suggests a need for improvement for future studies. As such, researchers should design methodologically robust studies that address the limitations discussed in this

review and examine new and important hypotheses. Proportionately lower scores on the external validity subscale implicate this as an area for investment to improve the overall quality of future research studies. Future research endeavors should be tuned to the importance of the external validity of results by implementing prospective studies that capture repeated measures on a population-based, representative random sample of individuals over time. In addition, important confounding factors should be measured and accounted for in the design and analysis phase of the study in order to present internally valid results. Such cohort investigations are needed to identify true risk factors and the nature of any causal relationships. It is with this next phase of research findings that we can identify potential targets for intervention that could be systematically evaluated in clinical practice. Such steps will help researchers and clinicians to better understand the experience of mothers with depressive symptoms and ultimately enhance the lives of children who are living with epilepsy.

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Table 2.1. 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 outcomes?
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?

Internal Validity (bias and confounding)

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 for confounding 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 2.2. Summary of Studies Reviewed.

Citation	Study Design	Sample	Measure	Results Reported	QIS
Adewuya, 2006 (Nigeria)	Cross-sectional Adolescents, mean age 14.4 years	N=86 Tertiary outpatient clinic; various seizure types	SDS	Child Outcomes	12
Adewuya & Ola, 2005 (Nigeria)	Cross-sectional Adolescents, mean age 14.5 years	N=102 Tertiary outpatient clinic; various seizure types	GHQ	Child Outcomes	11
Baki et al. 2004 (Turkey)	Cross-sectional Epilepsy (n=35): mothers, mean age 37.7 years children, mean age 12.8 years Controls (n=35): mothers, mean age 38.6 years children, mean age 12.7 years	N=70 Epilepsy (various seizure types): tertiary outpatient clinic Controls (age- and sex-matched): two local high schools	BDI	Prevalence Child Outcomes	9
Chiou & Hsieh, 2008 (Taiwan)	Cross-sectional, random and convenience samples Epilepsy (n=48): children, mean age 10.6 years Asthma (n=54): children, mean age 11.4 years	N=102 Tertiary outpatient clinics; various seizure types	PSI	Prevalence	10
Dunn et al. 1999 (United States)	Cross-sectional, convenience sample Children, mean age 14.4 years	N=115 Two tertiary outpatient clinics and private practices of neurologists and	CES-D	Prevalence Child Outcomes	13

		paediatricians; various seizure types			
Hoare, 1984 (United Kingdom)	Cross-sectional New-onset epilepsy (n=52): children, mean age 8.2 years siblings, mean age 9.4 years Chronic epilepsy (n=52): children, mean age 9.4 years siblings, mean age 10.8 years	N=104 Medical records and personal contact with regional paediatricians; various seizure types	GHQ	Child Outcomes	7
Hoare & Kerley, 1991 (United Kingdom)	Cross-sectional Mothers, mean age 37.0 years Children, mean age 10.4 years	N=108 Tertiary outpatient clinic; various seizure types	GHQ	Child Outcomes	8
Iseri et al. 2006 (Turkey)	Cross-sectional Mothers, mean age 35.6 years Children, mean age 9.5 years	N=80 Tertiary outpatient clinic; various seizure types	SCID	Prevalence	9
Mu et al. 2005 (Taiwan)	Cross-sectional, convenience sample Mothers, mean age 36.8 years Children, mean age 9.4 years	N=316 Tertiary outpatient clinic; various seizure types	BDI	Correlates	10
Mu et al. 2001 (Taiwan)	Cross-sectional Mothers, mean age 36.7 years Children, mean age 9.4 years	N=324 Three tertiary outpatient clinic; various seizure types	BDI	Correlates	9
Rodenburg et al. 2006	Cross-sectional Mothers, mean age 38.8 years	N=91 Tertiary outpatient clinic;	SDS	Prevalence Child	9

(Netherlands)	Children, mean age 8.4 years	various epilepsy syndromes		Outcomes	
Shore et al. 2004 (United States)	Cross-sectional Mothers, mean age 38.0 years Children, mean age 11.3 years	N=156 Two tertiary outpatient clinics and private practices of neurologists and paediatricians; various seizure types	MAACL-DS	Correlates	8
Shore et al. 2002 (United States)	Cross-sectional Mothers, mean age 39.0 years Children, mean age 14.4 years	N=115 Two tertiary outpatient clinics and private practices of neurologists and paediatricians; various seizure types	CES-D	Prevalence Correlates	9
Wood et al. 2008 (Canada)	Cross-sectional Children, mean age 9.8 years	N=52 Tertiary outpatient clinic; intractable epilepsy	BDI	Prevalence Correlates Child Outcomes	12
Yong et al. 2006 (China)	Cross-sectional Children, mean age 9.0 years	N=252 Tertiary outpatient clinic; various seizure types	HAD	Child Outcomes	10

BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; GHQ, General Health Questionnaire; HAD, Hospital Anxiety and Depression Scale; MAACL, Multiple Adjective Affect Checklist Depression Scale; MDS, maternal depressive symptoms; PSI, Parenting Stress Index; QIS, Quality Index score; SCID, Structured Clinical Interview for DSM-IV; SDS, Self-Rating Depression Scale.

Chapter Three

Do Depressive Symptoms Affect Mothers' Reports of Child Outcomes in Children with New-onset Epilepsy?[a]

Introduction

Due to the challenging nature of surveying children,[1] the use of a caregiver as a proxy reporter is common in paediatric health research despite its inherent limitations.[2] This is especially common when patient-reported outcomes are used as outcome measures in conjunction with physician-reported clinical endpoints. Valid assessments by informants (e.g., caregivers and physicians) are important in making appropriate medical decisions for children, particularly those with chronic illnesses. This is because discrepancies between informants due to biased ratings may confuse interpretation of findings, potentially compromising appropriate treatment.[3, 4]

In a recent comprehensive review, De Los Reyes and Kazdin examined the individual, family, and system characteristics that influence informant discrepancies.[5] Among these characteristics, caregiver depression was found to distort reports of child internalizing and externalizing behaviour problems. Specifically, depressed mothers demonstrated a negative bias, whereby they almost consistently reported worse child behaviour problems as compared to other informants, including teachers and the children themselves. This "depression distortion" was described by Richters but he argued that necessary and sufficient criteria for evidence of distortion were lacking for the majority of studies, including the absence of a gold standard and inappropriate use of statistical analyses.[6] The depression distortion hypothesis can be considered a specific case of informant

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discrepancy as a result of mothers' depressive symptoms. Some subsequent research, not affected by the limitations described by Richters, has provided more robust evidence supporting the depression distortion hypothesis.[7-13] For example, in the study by Najam et al., depressed mothers reported more cases of child behaviour problems compared to non-depressed mothers and the differences between mother and child reports were associated with the mothers' mental health status.[11] Similar results were obtained in a study by Chilcoat and Breslau, which demonstrated that depressed mothers overstated their child's behaviour problems compared to reports completed by the child's teacher.[8] The results from these studies suggest that depressed mothers' reports of their children's behaviour problems are biased towards over-reporting problems.

One notable gap in research to date is the relative lack of studies examining whether depressive symptoms in mothers affect their report of outcomes in which the child has a chronic illness. Though studies have been conducted in general population samples, we are aware of only two studies that have examined this issue within the context of chronic childhood illnesses.[12, 14] Because families with chronically ill children are often required to make many medical decisions, bias associated with caregiver reporting could potentially lead to treatment strategies that may not optimize outcomes for children. As well, given that caregivers of children with a chronic illness, such as epilepsy have a relatively high prevalence of depressive symptoms,[15] there may be a greater probability of depression distortion in these populations.

Also, assessments of the impact of mothers' depressive symptoms to date have tended to focus on maternal reports of child behaviour problems. No studies have examined the potential impact on other important parent-reported child outcomes, such as health-related quality of life, which have become increasingly common in clinical research.[16, 17] Health-related quality of life refers to the "subjective and objective impact of dysfunction associated with an illness or injury, medical treatment, and healthcare policy".[18] Investigators have commonly adopted

descriptions of four core domains of health-related quality of life: functional status, psychological functioning, social functioning, and disease state/symptoms.[18]

This study set out to investigate whether the presence of depressive symptoms in mothers affects their reports on their children's health-related quality of life in a sample of children with new-onset epilepsy. Childhood epilepsy is a relevant paediatric illness in which to examine the potential for this type of informant bias given that it is one of the most common neurological illness affecting children, with an estimated prevalence of 5/1000 children and incidence of 40-60/100,000 children per year in developed countries.[19] Also, epilepsy is a multifaceted condition requiring complex management and collaboration among patients, families, and physicians.[20] Since mothers, as the primary caregiver for the majority of young children, very often play the key role of proxy reporter in research on children with epilepsy it is imperative that the depression distortion hypothesis is examined prior to conducting additional analyses.

The objective of this manuscript was to assess whether there is evidence that mothers of children with new onset epilepsy experiencing symptoms of depression report differently on their children's health outcomes than mothers without symptoms of depression. If it is the case that depressed mothers' reports are negatively biased, this bias can be detected by comparing mothers' and neurologists' reports of children's health-related quality of life.

We hypothesized that maternal depressive symptoms would moderate the relationship between mothers' and neurologists' reports of children's functional status, psychological functioning, social functioning, and disease state/symptoms. That is, the association between mothers' and neurologists' reports would vary significantly when stratified by level of maternal depressive symptoms.

Methods

Sample and Data Source

Data for this study came from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES), a prospective cohort study designed to examine the determinants of health-related quality of life in children with epilepsy during the first 24 months post-diagnosis. Families were recruited from paediatric neurology sites across Canada and consisted of a sample of English-speaking families with a child diagnosed with epilepsy between 4-12 years of age. Participants were recruited over a 36-month period by a paediatric neurologist and provided written consent prior to being enrolled in the study. Primary caregivers were contacted by study investigators by telephone to determine participation status and sent self-administered questionnaires by mail at diagnosis (baseline), and six, 12, and 24 months. Of the 456 eligible families approached to participate in HERQULES, 443 (97%) provided written consent and 374 (82%) completed the baseline survey. For this study, only surveys completed at baseline by mothers (i.e., biological, adoptive, or foster) were analyzed. Of the baseline responses, 339 (91%) were completed by mothers. Ethical approval for HERQULES was obtained from all relevant research ethics boards across the country.

Measures

Mothers' Report

Maternal depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item questionnaire that measures depressive symptoms in the general adult population over the past week.[21] The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. The response values are four-point Likert scales (0-3), and anchor points in terms of days per week "rarely or none of the time (less

than one day)" to "most or all of the time (5-7 days)". The final score ranges from 0-60, with a higher score indicating greater impairment. Individuals with a final score of ≥16 are typically identified as having clinically relevant depressive symptomatology. In this sample, the internal consistency reliability was high (α=0.80).

Mothers completed the Quality of Life in Childhood Epilepsy (QOLCE) and the Child Health Questionnaire Parent Form-50 (CHQ). The QOLCE is a multifaceted, parent-report, epilepsy-specific instrument for evaluating health-related quality of life in children with epilepsy aged 4-18 years.[22] Item analysis and validation in North America led to a final questionnaire containing 76 items with 16 subscales spanning seven domains of life function including, physical activities, social activities, cognition, well-being, behaviour, general health, and general quality of life.[23] Items are rated on a five-point Likert scale, which are used to calculate the 16 subscale scores ranging from zero (low functioning) to 100 (high functioning). The subscale scores are averaged to produce an overall health-related quality of life score. In this sample it demonstrated very high internal consistency reliability (α=0.92).

The CHQ is a 50-item, parent-rated, generic questionnaire assessing child health, well-being, and the impact of illness on life function during the previous four weeks.[24] Each of the CHQ dimensions is measured with multiple items, with higher scores indicating better health-related quality of life. Nine concepts focus on the child, which include physical functioning; limitations in schoolwork and activities with friends due to emotional/behavioural difficulties; limitations in schoolwork and activities with friends due to physical health; bodily pain/discomfort; general behaviour; mental health; self esteem; general health perceptions; and change in health. The remaining four concepts measure impact on the family: parental impact-time; parental impact-emotional; family activities; and family cohesion. Two weighted and standardized summary scores assessing physical and psychosocial functioning are calculated, with a mean of 50 and a standard deviation of 10. The CHQ had very high internal consistency reliability in this sample (α=0.90).

Family functioning, resources, and demands were measured based on mothers' reports and used in the regression analyses to control for the confounding effect of family environment on depressive symptoms. The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR), was used to measure the perception of family functioning as assessed by a family member's self-report of satisfaction with the following five parameters: adaptation, partnership, growth, affection, and resolve.[25] The Family APGAR is a five-item instrument that uses a five-point Likert scale response option, with scores ranging from 0-4 for each item. Higher scores indicate higher satisfaction with family functioning. The Family APGAR has been found to be valid and reliable in both the clinical and research setting with adults and children.[25-27]

Family demands were quantified using the Family Inventory of Life Events and Changes (FILE), which assesses the pile-up of simultaneous normal and non-normal life events and changes in life events experienced by a family during the previous year.[28] The 71 items are grouped into nine scales assessing various strains: intra-family, marital, pregnancy/childbearing, finance and business, work-family transitions, illness and family care, losses, transitions in and out, and legal. The score is computed by giving each "yes" response a score of one. The reliability and validity of the FILE is well-established.[28]

The Family Inventory of Resources for Management (FIRM) was used to assess resources available to aid families' adaptation to stressful events.[29] For this study, only two scales (family mastery and health, extended family social support), which have been found to be associated with adaptation to childhood epilepsy, were used.[30] Scores on individual items, which range from 0 (not at all) to 3 (very well), are summed to provide a total FIRM score. The FIRM has demonstrated adequate reliability and validity properties.[29]

Socio-demographic information included date of birth (mother and child), child gender, number of children in household, parents' marital and employment status, level of education, and yearly household income.

Neurologists' Report

Paediatric neurologists completed the Global Assessment of Severity of Epilepsy (GASE), a single-item, seven-point global rating scale (1=extremely severe to 7=not at all severe) designed for neurologists to assess the overall severity of epilepsy in children, taking into account all aspects of the patient's epilepsy.[31] The GASE demonstrated minimum burden on participants, adequate validity, and high intra- and inter-rater reliability.[31] Paediatric neurologists assessed the extent to which epilepsy interferes with daily activities on a seven-point scale (1=none to 7=severe). Severity of child behaviour (0=none to 3=severe), cognitive (0=none to 4=severe), and motor problems (0=none to 3=severe), and other epilepsy characteristics such as seizure type, age of seizure onset, frequency/intensity of seizures, injuries during seizures, severity of post-ictal period, and side effects of anti-epileptic drugs were assessed by questions widely used in Canada previously by the Canadian Epilepsy Database Registry and items drawn from neurologists' forms used in testing the Impact of Pediatric Epilepsy Scale.[32, 33]

Procedure

Questionnaires used in HERQULES were reviewed by the investigators to identify several domains of child health on which both mothers and neurologists provided reports focusing on the four core domains of health-related quality of life. A total of 15 paired variables within these domains were identified for analysis and are described in Table 3.1. While the same specific measures were not completed by the two types of informants, it is reasonable to suggest that mothers' and neurologists' ratings on each individual domain would be similar. For the functional status domain, the cognition subscale of the QOLCE was regressed on a five-point (higher

scores indicate better functioning) neurologist assessment of child cognitive problems. As well, the QOLCE subscales physical restrictions and energy/fatigue and the CHQ subscales role-physical and physical functioning were regressed on a seven-point neurologist assessment of interference of epilepsy or treatment with daily activities (higher scores indicating fewer disruptions). For psychological functioning, the behaviour subscale of the QOLCE and the role-emotional/behaviour and behaviour subscales of the CHQ were regressed on a four-point (higher scores indicate better functioning) neurologist assessment of child behaviour problems. To assess social functioning, the QOLCE subscales social interactions, social activities and stigma were regressed on the neurologist assessment of interference of epilepsy or treatment with daily activities. In terms of disease state/symptoms, mother-reported overall QOLCE and CHQ (physical and psychosocial) summary scores were regressed on the neurologist-reported GASE (higher scores indicate less severity).

Statistical Analysis

Univariable analysis was used to describe the sample in terms of maternal mental health status using descriptive statistics and frequency distributions. In order to address limitations associated with dichotomizing mothers as depressed or non-depressed described by Richters[6] and to ensure that results were not an artifact based on other extraneous variables, tests of moderation using multiple regression analysis were performed with CES-D scores as a continuous measure of maternal depressive symptoms and were controlled for potential confounding maternal and family factors. Fifteen regression models were conducted whereby the mothers' report was the dependent variable [e.g., QOLCE (total)] and was regressed on the neurologists' report (e.g., GASE), mothers' depressive symptoms (CES-D), and an interaction term conceptualized as the product between neurologists' report and mothers' depressive symptoms (i.e., GASE×CES-D). The product term is included to determine whether the relationship between the mother report and the neurologist report is moderated by the mother's mental health status. A statistically significant

product term indicates that mothers with lower versus higher levels of depressive symptoms differ in the extent to which their reports are similar to neurologists' reports. In the presence of a statistically significant product term, a conditional moderator variable based on CES-D scores and the standard deviation of the sample was used in subsequent *post hoc* regression analyses as described by Holmbeck to probe interactions and further describe the effect of mothers' depressive symptoms on their reports.[34] With a sample size of 339, this study was adequately powered to detect significant interaction effects (i.e., change of six points on the CES-D) with 1-β=0.80 at α=0.05. Data analysis was conducted with Statistical Analysis Software (SAS 9.1.3 Service Pack 4, SAS Institute Inc., Cary, NC).

Results

Sample Characteristics

A total of 339 mothers participated in this study. Baseline characteristics of the study sample are shown in Table 3.2. Briefly, mothers had a mean age of 37.9 (standard deviation 5.9) years. Sixty-nine percent were college/university graduates and 66% were employed. Approximately 80% of mothers were married. Mothers' overall mean score on the CES-D was 14.6 (10.5) and 37.7% of mothers were at risk for clinical depression based on a CES-D score ≥16. The mean age of their children was 7.9 (2.3) years and 52% were male. Mean scores on the QOLCE, CHQ (physical), CHQ (psychosocial), and GASE were 69.8 (13.8), 48.6 (10.6), 44.4 (10.8), and 5.5 (1.2), respectively. Neurologist reports indicated that 15% of children had behaviour problems, 18% had cognitive problems, and 55% had disruptions in daily activities as a result of epilepsy or its treatment. Mean scores describing the family environment were as follows: Family APGAR 13.9 (3.8), FILE 9.9 (6.6), and FIRM 49.8 (11.1). Approximately 36% of families had a total household income of ≥$80,000 per year. These results describe families that were, on average, functioning well, had low stress, adequate resources, and had high socio-economic status.

Effect of Mothers' Depressive Symptoms on Reporting

To examine whether mental health status moderated mothers' reports of children's health-related quality of life, a series of multiple regression analyses was conducted. The regression analyses were controlled for the potentially confounding effects of mothers' age, education, employment status, marital status, family functioning, stress/demands, social resources, and income, as these factors are theoretically linked and empirical evidence has shown to be associated with depression.[35, 36] Results of the regression analyses are shown in Table 3.3. In order to ensure that the null findings were not the result of controlling for these psychosocial factors known to be associated with depressive symptoms, additional unadjusted (regression model excluded all potential confounders) and partially adjusted (regression model included only the following potential confounders: mothers' age, education, employment status, and marital status) were conducted. The results were similar to those reported in Table 3.3 and thus are not presented. Only one significant product term was observed in the functional status domain for disruptions in daily activities×CES-D (β=0.24, p=0.008) when modeling QOLCE (energy/fatigue), and subsequently underwent subsequent *post hoc* probing of the interaction effect.

The results of the *post hoc* analysis suggest that mothers with low levels of depressive symptoms report similar outcomes as neurologists when evaluating disruptions in daily activities due to the child's epilepsy. That is, as neurologists report better functioning, so do mothers. In contrast, mothers with high levels of depressive symptoms systematically report higher scores on the QOLCE (energy/fatigue) subscale (indicating little disruptions in activities due to energy/ fatigue) for children with both high and low scores of neurologist-reported disruptions in daily activities. The results of the *post hoc* analysis are shown in Figure 3.1.

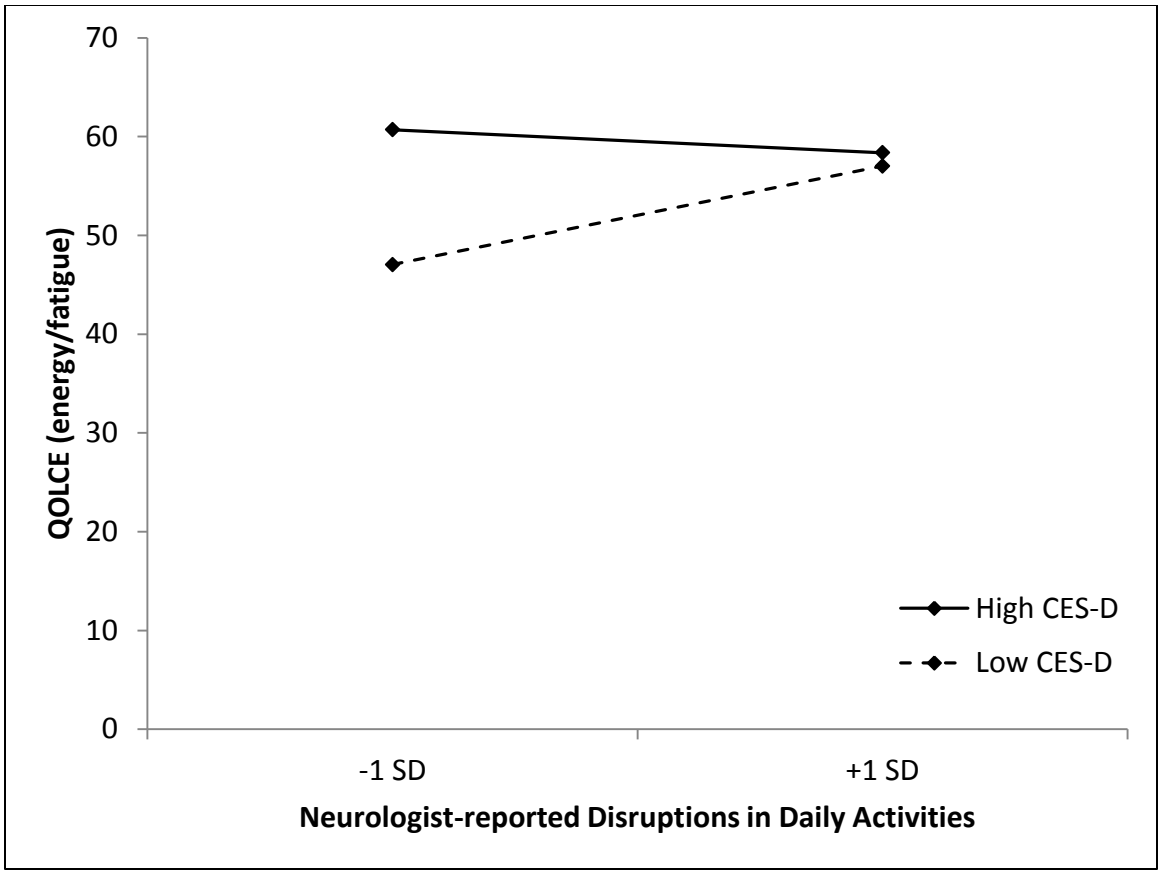

Figure 3.1. Effect of Maternal Depressive Symptoms on Reporting the Impact of Epilepsy on Disruptions in Daily Activities in Children. The results suggest that mothers with high scores on the Center for Epidemiological Studies Depression Scale (CES-D), consistently report elevated scores on the energy/fatigue subscale of the Quality of Life in Childhood Epilepsy (QOLCE). SD, standard deviation.

Discussion

This is the first study to examine whether depressive symptoms in mothers affects reporting on children with new-onset epilepsy. Results of this study did not provide evidence that mothers' reports of child outcomes are affected by depressive symptoms. Multiple regression analyses of the four domains of health-related quality of life: functional status, psychological functioning, social functioning, and disease state/symptoms, did not yield statistically significant estimates for the interactions between mothers' and neurologists' report of child outcomes, except for the regression of mothers' assessments of their child's energy/fatigue and its impact on daily activities in the functional status domain. The unbiased estimates

produced through the control of confounding factors in multiple regression offers a higher level of evidence than the estimates used in previous studies to indicate a lack of evidence to support the depression distortion hypothesis. Overall, this suggests that depressed mothers are not more likely to give biased reports of their child's outcomes.

Though evidence for depression distortion in the general population has been mixed,[6] results from studies in other paediatric chronic illnesses support the hypothesis.[12, 14] In a study by Chi and Hinshaw, levels of depressive symptoms in mothers of children with attention deficit/hyperactivity disorder predicted negative biases in mothers' reports of children's illness symptoms and behaviour problems.[12] Recently, Hood examined the depression distortion hypothesis in a sample of caregivers whose children were diagnosed with type-1 diabetes.[14] Hood demonstrated that caregivers with elevated depressive symptoms systematically rated high levels of depressive symptoms in the youth, whereas caregivers with lower depressive symptoms reported similar levels as the youth themselves.

There was only one exception to the finding that mothers with elevated depressive symptoms differed in the extent to which mothers' reports were related to neurologists' reports, which was for how the child's level of energy/fatigue interrupted their daily activities. This may be attributable to depressed mothers being less aware of how energy levels affect daily functioning in their child given their concern with their own depressive symptoms. Thus, mothers with elevated depressive symptoms may under-estimate the impact of energy levels in children with epilepsy. However, given that 15 regression models were examined, one must consider that this significant finding may be the result of the multiple testing problem. The multiple testing problem occurs when one considers a set of statistical inferences simultaneously. Errors in inference, including hypothesis tests that incorrectly reject the null, are more likely to occur when one considers the set of inferences as a whole.[37] Indeed, when the Bonferroni correction ($\alpha/15=0.003$) is applied to this set of regression models to account for the multiple testing problem,

the null hypothesis is not rejected, suggesting that mothers with elevated depressive symptoms do not provide discrepant reports on how their child's energy/fatigue may disrupt daily activities.

The fact that there were no other significant findings was unlikely to be the result of missing important effects since the study was adequately powered to detect statistically significant and clinically relevant interaction effects, as described by McCarthy[38] and Wyrwich.[39] As well, research has shown that discrepancies due to depressive symptoms are more apparent when examining negative attributions as compared to positive attributions.[40, 41] The fact that the current study focused on negative aspects of the illness process, especially behaviour and cognitive problems, and disruptions in daily activities, offers some assurance that it presented the opportunity to detect discrepancy in reporting of negative attribution should it have been present. Since families dealing with incident cases of childhood epilepsy were recruited, it is possible that mothers may have been highly attuned to their child's illness and related symptoms, regardless of their mental health status. Whether support for informant discrepancy may be found in a sample of prevalent cases of childhood epilepsy remains to be elucidated.

The results of this study are tempered by several limitations. First, the sample under study was recruited from paediatric neurology practices that may not be representative of all families with a child with epilepsy, thus potentially limiting external validity. However, there are feasibility constraints in designing population-based studies. In the absence of population-based registries for epilepsy to facilitate such studies, Speechley et al. demonstrated that it may be feasible to recruit a representative population-based sample of children with epilepsy by targeting paediatric neurologists.[42] In this study, family physicians practicing in southwestern Ontario, reported they would refer between 80-99% of their patients with childhood epilepsy (depending on the type of seizure and syndrome) to a paediatric neurologist.

Second, there are some limitations associated with the measures used in the study. Although the CES-D is a valid, reliable, and widely used measure, it is a self-report screening measure of psychological distress rather than a diagnostic instrument for clinical depression.[43] Also, mothers and neurologists did not complete the same measures so we cannot be certain that the two groups were reporting on identical constructs, which may have masked evidence for distortion. As well, for several of the neurologists' assessments of individual domains of health-related quality of life were based on a single-items measure, which can be viewed as problematic. However, research has shown that in certain circumstances, multi-item measures do not perform better than a single-item measure, prompting the recommendation that the appropriateness of a single-item measure be evaluated by assessing its psychometric properties prior to rejecting its practicality.[44, 45]

Third, while not feasible in the current study, self-report for children old enough would have been helpful. Although mothers may have a better understanding of the health issues being examined and the content of questionnaires compared to children, the young patient's experience with illness should also be acknowledged in future investigations.

A question arises from this research. If we had found that mothers' depressive symptoms affected their reports of children's health-related quality of life, would the magnitude of bias be clinically relevant? A study by Sawyer et al. concluded that in community samples the size of bias in caregivers' reports of child behaviour problems due to parental distress was likely to be quite small and of little clinical significance.[46] However, this study was conducted in a general community sample and whether the results can be extrapolated to chronically ill child populations is unknown.

Conclusion

This study did not find evidence to support that depressive symptoms affect mothers' reports of child outcomes. The results from this study suggest that mothers of children with new-onset epilepsy, regardless of their mental health status are valid informants for various aspects of their child's health outcomes. Future investigations examining informant discrepancy are needed and should implement methodologically rigorous designs with multiple informants, including child reports, in order to acquire a more thorough understanding of this phenomenon.

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Table 3.1. Domains of Health-related Quality of Life as Reported by Mothers and Neurologists.

Domain	Parent Measure	Neurologist Measure
Functional Status	QOLCE (cognitive) 22-item subscale; attention, concentration, language, and memory QOLCE (physical restrictions) 10-item subscale; physical activities QOLCE (energy/fatigue) 2-item subscale; energy levels CHQ (physical functioning) 6-item subscale; physical activities CHQ (role physical) 2-item subscale; limitations due to physical health	Cognitive Problems Single-item, 5-point scale rating level of cognitive disability Disruptions in Daily Activities Single-item, 7-point scale rating interference of epilepsy with daily activities
Psychological Functioning	QOLCE (behaviour) 16-item subscale; behaviour CHQ (role emotional/behaviour) 3-item subscale; limitations due to behaviour CHQ (behaviour) 5-item subscale; describing behaviour problems CHQ (global behaviour) Single-item scale; overall behaviour compared to other children	Behaviour Problems Single-item, 4-point scale rating level of behaviour problems
Social Functioning	QOLCE (social interactions) 5-item subscale; problems with social interactions QOLCE (social activities) 3-item subscale; limitations in social activities QOLCE (stigma) Single-item scale; effect of epilepsy stigma on social activities	Disruptions in Daily Activities Single-item, 7-point scale rating interference of epilepsy with daily activities
Disease State/ Symptoms	QOLCE (total) Total score of quality of life subscales CHQ (physical) Summary score of physical subscales CHQ (psychosocial) Summary score of psychosocial subscales	GASE Single-item, 7-point scale rating overall severity of epilepsy

Table 3.2. Characteristics of the Study Sample.

Characteristic	
Mother	
Age, years	37.9 (5.9)
University Graduate, n (%)	203 (69.3)
Employed, n (%)	223 (66.4)
Married, n (%)	270 (79.7)
CES-D	14.6 (10.5)
Child	
Age, years	7.9 (2.3)
Male, n (%)	175 (51.6)
Health-related Quality of Life	
QOLCE	69.8 (13.8)
CHQ, Physical	48.6 (10.6)
CHQ, Psychosocial	44.4 (10.8)
Illness Severity, GASE	5.5 (1.2)
Behaviour Problems, n (%)	51 (14.6)
Cognitive Problems, n (%)	62 (18.0)
Disruptions in Daily Activities, n (%)	186 (54.8)
Family	
Functioning, Family APGAR	13.9 (3.8)
Demands, FILE	9.8 (6.6)
Resources, FIRM	49.8 (11.1)
Income ≥$80,000, n (%)	118 (36.3)

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

Table 3.3. Tests of Interaction Examining the Presence of Depression Distortion in Mothers' Reports of Child Health-related Quality of Life.*

Outcome	Model F†	Model R^2	β for Interaction	Standard Error	95% Confidence Interval
Functional Status					
QOLCE (cognitive)	6.46	0.21	0.05	0.14	-0.23, 0.33
QOLCE (physical restrictions)	3.18	0.12	0.02	0.09	-0.15, 0.19
QOLCE (energy/fatigue)	2.76	0.10	0.24	0.09	-0.06, 0.41
CHQ (physical functioning)	4.44	0.15	0.04	0.08	-0.11, 0.19
CHQ (role physical)	2.86	0.10	0.10	0.11	-0.12, 0.32
Psychological Functioning					
QOLCE (behaviour)	9.96	0.27	-0.14	0.12	-0.38, 0.10
CHQ (role emotional/behaviour)	7.12	0.21	-0.19	0.20	-0.59, 0.20
CHQ (behaviour)	10.45	0.28	-0.12	0.13	-0.37, 0.14
CHQ (global behaviour)	10.64	0.28	-0.52	1.80	-4.06, 3.02
Social Functioning					
QOLCE (social interaction)	4.02	0.14	-0.08	0.10	-0.12, 0.28
QOLCE (social activities)	3.20	0.11	-0.02	0.11	-0.25, 0.20
QOLCE (stigma)	4.47	0.15	0.00	0.13	-0.26, 0.25
Disease State/Symptoms					
QOLCE (total)	6.15	0.20	0.11	0.07	-0.03, 0.25
CHQ (physical)	3.05	0.11	0.01	0.05	-0.09, 0.12
CHQ (psychosocial)	9.05	0.27	0.11	0.23	-0.34, 0.56

*Regression analyses were controlled for maternal age, education, employment status, marital status, and family functioning, resources, and demands.

†All models had 11 degrees of freedom and were statistically significant at $p<0.003$.

Chapter Four

Prevalence and Trajectories of Depressive Symptoms in Mothers of Children with Newly-diagnosed Epilepsy[a]

Introduction

Caring for a child with a chronic illness can be a significant source of stress for parents. Similar to other childhood chronic illnesses or disorders, the impact of epilepsy is not limited to the child having seizures, but affects all members of the family to a certain degree.[1-3] Compared to families of healthy children, families of a child with epilepsy have been found to experience significantly more stress, anxiety, and restrictions in family life,[2] higher levels of dissatisfaction with their social situation, lower levels of marital satisfaction and support,[3] and lower quality parent-child relationships and poor family adaptation.[4] Since mothers are most often primarily responsible for children's care,[5] they might be particularly at risk for psychological distress in response to their child's epilepsy, most notably depression.[6, 7]

In the past decade, six studies investigated depressive symptoms in mothers of children with epilepsy.[8-13] A recent systematic review of studies examining depressive symptoms in mothers of children with epilepsy showed that prevalence estimates vary widely with between 12% and 49% of mothers scoring at or above the cutoffs for clinical depression based on self-report screening measures.[14] Previous studies were affected by limitations in study design including a lack of prospective cohort studies, inclusion of non-representative samples, and sampling procedures prone to selection bias. No study has examined maternal depressive symptoms prospectively and none has focused on mothers of children with newly-diagnosed epilepsy.

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[a]A version of this section was published elsewhere as, Ferro MA, Avison WR, Campbell MK, Speechley KN. Prevalence and trajectories of depressive symptoms in mothers of children with newly-diagnosed epilepsy. Epilepsia 2011;52(2):326-36.

Given the paucity of research in this area, the objectives of this paper were to: 1) estimate the prevalence of depressive symptoms among mothers of children with new-onset epilepsy at diagnosis and six, 12, and 24 months after diagnosis; 2) identify trajectories of maternal depressive symptoms; and, 3) examine predictors of depressive symptom trajectories.

Methods

Sample and Data Source

Data for this study came from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES), a prospective cohort study designed to examine the determinants of health-related quality of life in children with epilepsy during the first 24 months post-diagnosis. Paediatric neurologists across Canada seeing children with new-onset epilepsy approached parents of eligible patients about the study. Inclusion criteria were: new case of epilepsy (≥2 unprovoked seizures) in a child 4-12 years of age, in whom a diagnosis had not been confirmed previously, seen for the first time by a participating paediatric neurologist; and parent/caregiver, with sufficient English language skills, who had been primarily responsible for the child's care for at least the past six months and continued to be for the duration of the study. Exclusion criteria were: diagnosis of epilepsy that had been previously confirmed by another physician; and diagnosis of other progressive or degenerative neurological disorder (e.g., mental retardation) or other major co-morbid non-neurological disorders that would have an impact on quality of life (e.g., asthma requiring daily medication, renal failure). Parents who agreed to provide their address for the purpose of this research were mailed a letter describing the study and outlining what their participation would entail. Specifically, participants were asked to complete four mailed questionnaires designed for self-administration [time 1: after diagnosis (baseline), time 2: at six months, time 3: at 12 months, and time 4: at 24 months], as well as provide informed consent for their child's neurologist to complete a brief form providing relevant clinical information. Of the

456 eligible families approached to participate in HERQULES, 443 (97.1%) verbally consented. Of these, 374 (83.7%) completed the baseline survey. For this paper, only surveys completed by a child's mother (i.e., biological, adoptive, or foster mother) were used in the analysis [n=339 (91.0%)]. Approval for HERQULES was obtained from all relevant research ethics boards across the country and parents provided written consent.

Measures

Maternal Depressive Symptoms

Level of depressive symptoms in mothers was measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item questionnaire designed to assess depressive symptoms in the general adult population over the past week.[15] The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. A four-point Likert scale (0-3) is used to rate the frequency of symptoms experienced, ranging from "rarely or none of the time (less than one day)" to "most or all of the time (5-7 days)". The total score spans from 0-60, with a higher score indicating greater level of depressive symptoms. Individuals with a total score of ≥16 are typically identified as being at risk for clinical depression. Among community samples, internal consistency estimates for the CES-D ranged from 0.8-0.9[15] and in this sample, estimates ranged from 0.75-0.80.

Child Health-related Quality of Life

Child health-related quality of life was reported by mothers using the Quality of Life in Childhood Epilepsy (QOLCE).[16] The QOLCE is a multifaceted, parent-report instrument for evaluating health-related quality of life of children with epilepsy aged 4-18 years. The QOLCE contains 76 items with 16 subscales spanning seven domains of life function including, physical activities, social activities, cognition,

well-being, behavior, general health, and general quality of life.[16] Items are rated on a five-point Likert scale, which are used to calculate the 16 subscale scores ranging from zero (low functioning) to 100 (high functioning). The subscale scores are averaged to produce an overall health-related quality of life score. It has demonstrated good construct validity, internal consistency reliability, and sensitivity to epilepsy severity.[17] The internal consistency reliabilities were excellent for all measurement occasions in this sample (0.92-0.94).

Epilepsy Characteristics

Physicians completed a questionnaire documenting the clinical factors of each patient's epilepsy including: severity of epilepsy, seizure type and frequency, type of epilepsy syndrome, age at onset and diagnosis, medication information, and adverse effects. Neurologists were also asked to rate the presence of comorbidities using single-item measures, specifically, any behavior (0=none to 3=severe), cognitive (0=none to 4=severe), or motor problems (0=none to 3=severe). Severity of epilepsy was classified using the Global Assessment of Severity of Epilepsy (GASE), a single-item measure developed for HERQULES.[18] With the GASE, neurologists rate the overall severity of each child's epilepsy using a seven-point scale ranging from 1=extremely severe to 7=not at all severe. The GASE was quick and easy to complete, demonstrated adequate validity, and high intra- and inter-rater reliability.[18]

Family Environment

Three aspects of the family environment (functioning, resources, and demands) were measured based on parent-report. The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR) was used to assess satisfaction with family relationships.[19] The Family APGAR is a five-item instrument where responses are based on a five-point Likert scale, ranging from 0-4 for each item, with higher scores indicating higher satisfaction with family functioning. The Family APGAR has

been found to be valid and reliable in both the clinical and research setting with adults and children.[19-21] The internal consistency reliabilities ranged from 0.86-0.89 in this sample.

The Family Inventory of Resources for Management (FIRM) was utilized to assess resources available to aid families' adaptation to stressful events.[22] For this study, only two subscales (family mastery and health, extended family social support), which have been found to be associated with adaptation to childhood epilepsy, were used.[23] Scoring procedures for the FIRM involve summing all response values, which range from 0 (not at all) to 3 (very well), to provide a total FIRM score. The FIRM has demonstrated adequate reliability and validity properties.[22] Internal consistency reliabilities in this sample ranged from 0.91-0.93 for the Family Mastery and Health subscale and 0.44-0.54 for the Extended Family Social Support subscale.

Family demands were quantified using the Family Inventory of Life Events and Changes (FILE), which assesses the accumulation of simultaneous normal and non-normal life events and changes in life events experienced by a family during the previous year.[24] There are 71 items in the FILE with the score computed by giving each "yes" response a score of one. Summing responses provides a score for each subscale and the total FILE score. The reliability and validity of the FILE is well-established.[24] As measured by Cronbach's α, the overall reliability of the FILE ranged from 0.98-0.99 in this sample.

Socio-demographic information was also collected including date of birth (mother and child), child gender, number of children in household, parents' marital and employment status, highest level of completed education, and total annual household income.

Perception of Patient-centered Care

A modified version of the Patient Perception of Patient-centeredness (PPPC) questionnaire, based on the Patient-Centered Model of Care, was used to assess mothers' perceptions of the extent to which the healthcare services her child received were patient-centered.[25] Seven of the original 14 items were slightly modified to make them appropriate for parent-report by replacing "your" with "your child's" and "you" with "your child". The PPPC is scored so that low scores correspond to positive perceptions. Inter-item reliability has been found to be adequate for the PPPC and evidence for convergent validity was examined with a significant correlation with the Measure of Patient-centered Communication.[26] In this sample, the internal consistency ranged from 0.77-0.86.

Statistical Analysis

Univariable analyses used to describe maternal depressive symptoms at each measurement occasion included descriptive statistics and frequency distributions. Bivariable analyses (*t*- and χ^2-tests) were used to compare mothers who completed the 24-month follow-up with those who did not complete the study.

Trajectories of self-reported maternal depressive symptoms, as measured by the CES-D, during the first 24 months after having a child diagnosed with epilepsy were investigated with a semi-parametric group-based approach (latent class growth modeling).[27] The essence of this method is to use polynomial functions to identify unobserved patterns of depressive symptoms over time. Through this approach, distinctive growth trajectories are identified. The degree to which an individual's trajectory resembles the prototypic trajectory is estimated and individuals are categorized into trajectory groups based on the similarity of the individual trajectory to the prototypic trajectories. A censored normal model was fitted to the data since there were a number of mothers who exhibited no or few depressive symptoms, resulting in a cluster of data at the scale minimum. The number of

groups to be included in the model is guided by *a priori* expectations, overall model fit based on the Bayesian Information Criterion (BIC), and posterior probability scores for each trajectory group. The model with the maximum BIC, optimized probability scores, and least number of groups is selected. The modeling process followed the strategy of Campbell, et al.,[28] whereby cubic trajectories were specified for three groups being examined and additional groups were added to the model and the change in BIC scores examined to determine the best model. In order to ensure model parsimony (i.e., most statistically efficient model), non-significant higher-order terms (i.e., quadratic and cubic) were removed and the model was respecified until optimal fit was achieved.[29]

Maternal, child, and family characteristics were compared across trajectory groups using analysis of variance for continuous variables and χ^2-tests for categorical variables. The Bonferroni correction was applied for multiple comparisons. Pairwise group contrasts (*post hoc* Scheffé or χ^2-test, when appropriate) were examined only if a statistically significant overall difference was observed across trajectory groups.

Multinomial logistic regression was conducted to identify predictors of depressive symptom trajectory using baseline data. A backward, stepwise selection approach using maternal, child, and family characteristics was utilized. Only variables that were statistically significant in the bivariate comparisons were included in the regression analysis. In order to generate a robust model, the condition for variables to enter and remain in the model was set at α=0.20.[30] Continuous variables in the model were categorized into quartiles to increase interpretability of the model. Data analysis was conducted with Statistical Analysis Software (SAS 9.1.3 Service Pack 4, SAS Institute Inc., Cary, NC). Group-based trajectory modeling was conducted with PROC TRAJ as described by Jones, et al.[31] All hypothesis tests were two-sided.

Results

Sample Characteristics

Of the 339 mothers in the study, 258 completed all four measurement occasions and 81 were lost during follow-up. Mothers who did not complete the study were more likely to be younger (p=0.0002), unmarried (p=0.0040), less educated (p=0.0122), have lower household income (p=0.0191), and more likely to have a child rated by his/her neurologist as having cognitive problems (p=0.0146) at baseline compared to mothers who remained in the study (Table 1). In addition, those who were lost to follow-up had more depressive symptoms (p=0.0152), fewer family resources (p=0.0206), and more family demands (p=0.0211) at baseline compared to those mothers who completed the study.

Mothers had a mean age of 37.7 (5.8) years at baseline. Approximately half of the children were male (52.2%). Children had a mean age of seizure onset of 6.9 (2.5) years and a mean age of 7.4 (2.4) years at baseline. Children had a mean score of 70.4 (13.4) on the QOLCE and the majority of children (58.7%) had "a little severe" or "somewhat severe" epilepsy severity score based on the GASE. Means scores on family environment measures were as follows: Family APGAR, 14.0 (3.8); FIRM 50.1 (11.1); and, FILE 9.6 (6.5). Additional baseline characteristics of the study sample are shown in Table 4.1.

Prevalence of Depressive Symptoms

Mothers' mean CES-D score was 14.6 (10.6) at baseline; 11.7 (9.5) at six months; 12.2 (9.7) at 12 months; and, 12.0 (10.0) at 24 months. At baseline, 37.9% of mothers scored as being at risk for clinical depression. This proportion changed to 29.9% at six months, 31.5% at 12 months, and 29.5% at 24 months.

Trajectories of Change in Depressive Symptoms

Based on model fit indices, a four- or five- group model was most appropriate. The BIC scores for the four- and five-group models were -15320.25 and -15227.58, respectively. The four-group model was adopted for the analysis not only in the interest of parsimony (i.e., most statistically efficient model), but also because the posterior probabilities of group membership were superior for the four-group model (0.84-0.96, mean=0.89) compared to the five-group model (0.82-0.91, mean=0.86).

Estimates for the four-group model parameters are shown in Table 4.2. Inspection of parameter estimates for the model revealed significant variation in the intercept across groups (F=25.05, p<0.0001). In other words, each group had a significantly different CES-D score at baseline. Groups one and two were observed to have two points of inflection (i.e., the point where the trajectory changes from increasing to decreasing or *vice versa*). Although it was more pronounced in group two, both groups were best modeled with the inclusion of a cubic term to represent time in order to capture these *S*-shaped trajectories. Group three had only one inflection point and was best modeled with the inclusion of a quadratic time term to capture the concave nature of the trajectory. Group four required the inclusion of a simple linear time term only since the trajectory continued in one direction (i.e., decreasing). Figure 4.1 depicts the four distinct trajectories of maternal depressive symptoms identified in the analysis. As indicated in Figure 1, the predicted and observed trajectories appear to correspond well with each other, suggesting that the data fit the model well.

The first trajectory identified was one of consistently low levels of depressive symptoms (*low stable*). Almost two-thirds of the sample (n=201, 59.3%) fell into this trajectory, with a mean CES-D score of 8.3 at baseline, which decreased to 7.2 at 24 months. The second trajectory included 25.1% (n=85) of the sample and is described as having *borderline* symptoms. These mothers had variations in

depressive symptoms during the 24-month follow-up that straddle the cut-off score (CES-D ≥16) indicating risk for clinical depression. The third trajectory (n=29, 8.6%) described a group of mothers that had a *moderate increasing* symptom trajectory that was relatively stable during the first 12 months of follow-up, then increased from 12 to 24 months. The fourth trajectory identified included mothers with a *high decreasing* trajectory (n=24, 7.1%). The mean CES-D score at baseline in this group was 37.7 which decreased to 18.1 at 24 months. CES-D scores for each group during the 24-month follow-up are shown in Table 4.3.

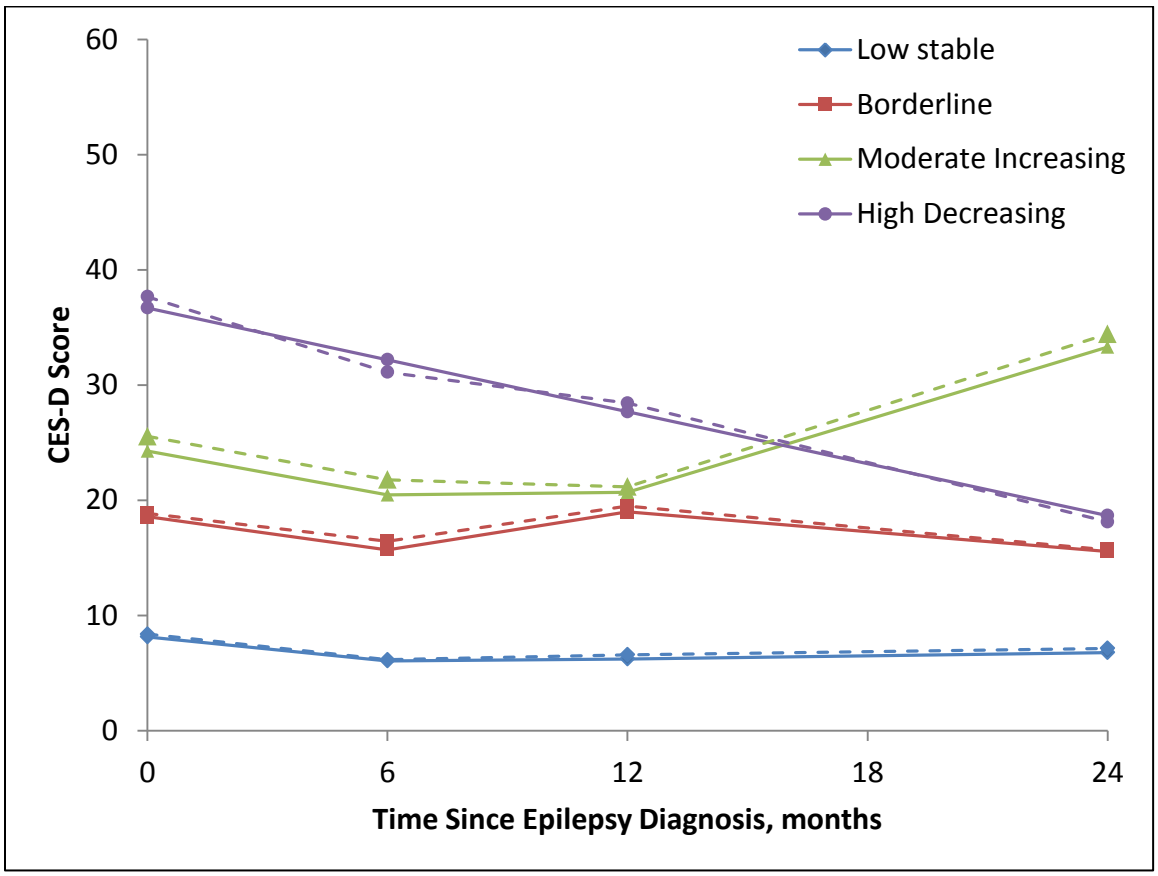

Figure 4.1. Trajectories of Maternal Depressive Symptoms during the First 24 Months after having a Child Diagnosed with Epilepsy. Solid lines depict observed trajectories and dashed lines predicted trajectories. CES-D, Center for Epidemiological Studies Depression Scale.

Predictors of Depressive Symptoms Trajectories

Maternal, child, and family characteristics were compared across trajectory groups and results are summarized in Table 4.4. Statistically significant overall effects were observed for maternal age (p=0.0001), marital status (p=0.0008), educational attainment (p<0.0001), child health-related quality of life (p<0.0001), and family functioning, resources, and demands (p<0.0001). Mothers in the *low stable* group were more likely to have higher education, children with better health-related quality of life, and families with better functioning, more resources, and fewer demands compared to the other trajectory groups. In pairwise contrasts, mothers in the *low stable* and *borderline* group were significantly more likely to be married compared to both the *moderate increasing* and *high decreasing* group. Mothers in the *borderline* group were significantly more likely to have fewer family demands compared to both the *moderate increasing* and *high decreasing* groups. In addition, the *borderline* group had significantly higher educational attainment, better child health-related quality of life, and more family resources compared to the *high decreasing* group. Mothers in the *moderate increasing* group were significantly younger compared to the *low stable* group.

Predictors of depression symptom trajectory were examined with multinomial logistic regression. Odds ratios using the *low stable* group as the reference category are summarized in Table 5. Briefly, the *borderline* group was younger (OR=0.53, p=0.0284), had worse family functioning (OR=0.65, p=0.0101), and fewer family resources (OR=0.50, p=0.0003). The *moderate increasing* group was also younger (OR=0.31, p=0.0141), had children with cognitive problems (OR=9.29, p=0.0043), worse family functioning (OR=0.50, p<0.0202), and more family demands (OR=4.00, p=0.0013). The *high decreasing* group had less education (OR=0.38, p=0.0005) and lower QOLCE scores (OR=0.42, p=0.0148) compared to the *low stable* group.

Discussion

This study used group-based trajectory modeling, a robust statistical method to identify trajectories of distinct subgroups within a population over time. Whereas traditional growth curve modeling is generally most useful for investigating research questions in which all individuals are hypothesized to change in a homogeneous trajectory over time,[32] some phenomena, such as depressive symptomatology, may exhibit a multinomial pattern whereby inter-individual variation may exist in both the magnitude and direction of change.[27, 28, 32] In such circumstances traditional growth curve modeling can mask significant differences and lead to erroneous inferences about changes in population over time. Thus, group-based trajectory modeling which considers potential multinomial heterogeneity in change over time was implemented.

Approximately 90% of surveys were completed by a maternal primary caregiver indicating that it is predominately mothers who assume the primary caregiving responsibility for children with epilepsy. This is consistent with previous child health reports in Canada, where it is the mother who performs the role of primary caregiving to children in the vast majority of cases.[33] Findings describing the family environment in our sample of families with a child with epilepsy were similar to other samples of children with a chronic illness,[24] but less favourable compared to families of healthy children.[34] For example, in a study of families with healthy children aged 4-15 years, 95% scored above 10 on the Family APGAR, a measure of satisfaction with family functioning,[34] compared to only 81-85% in the current sample. The extent to which families have experienced an accumulation of life events in the past year, as measured by the FILE, was quite similar in the current sample compared to a sample of families with a child with diabetes (9.6 vs. 10.5).[24]

Mothers' depressive symptoms, based on the CES-D and assessed at four times over the 24 months following the diagnosis of epilepsy, were significantly higher than those reported in a sample of mothers with a healthy child aged 4-10 years

(p=0.0017).[35] The proportion of mothers at risk for clinical depression ranged from 30% to 38% during the four measurement occasions. These results represent two-fold higher prevalence rates compared to mothers of healthy preschool children whose estimates ranged from 14% to 17% during the years leading to school-age.[36]

Four distinct trajectories of depressive symptoms in mothers of children with new-onset epilepsy were identified during the first 24 months after epilepsy diagnosis. The shapes of trajectories in this sample were similar to several of the trajectories identified by Campbell, et al. in their study of depressive symptoms in mothers of children prior to school entry.[28] The socio-demographic differences (e.g., maternal age, education, and income) across groups reported by Campbell, et al. were not observed in the current study, however. The largest group consisted of mothers with *low stable* CES-D scores who generally had more favourable characteristics (i.e., better child health-related quality of life, and a more positive family environment) compared to the other trajectory groups. The second largest group consisted of mothers with *borderline* depressive symptoms that varied over time and straddled the CES-D cut-score for risk of clinical depression. This trajectory pattern is consistent with current research documenting the periodic recurrence of depression in a large proportion of women.[37] The next largest group was composed of mothers with *moderate increasing* depressive symptoms during the 24-month follow-up. The smallest group consisted of mothers with *high decreasing* depressive symptoms. This declining trajectory is consistent with previous research documenting high initial levels of maternal depressive symptoms at child diagnosis that diminish over time[38-42] and with research that suggests resilience among adults experiencing trauma is a common response to an adverse event, in this case having a child diagnosed with epilepsy.[43] Interestingly, both the *moderate increasing* and *high decreasing* trajectory groups were observed to have significantly elevated depressive symptoms at each measurement occasion compared to the *low stable* group.

The multinomial predictive model demonstrated that baseline maternal age and education, child health-related quality of life, child cognitive problems, and family functioning, resources, and demands play an important role in determining membership in a specific depressive symptom trajectory. Having a child with cognitive problems was the strongest risk factor in the model, significantly predicting membership in the *moderate increasing* trajectory group. Such results may be useful for healthcare professionals since they demonstrate that strong predictors can be obtained using efficient measures that are well-suited for use in clinical settings. It was not surprising that epilepsy severity did not predict depressive symptom trajectory. This study included children aged 4-12 years with relatively less severe and stable epilepsy and showed little variation among children and over time. Previous research has shown that children with an earlier age of onset tend to have less favourable prognoses.[44] The absence of correlation between epilepsy severity and the trajectory of mothers' depressive symptoms may be attributable to the fact that the age group studied tends to exclude the most catastrophic epilepsies.

This predictive model may be useful for healthcare professionals in developing a psychosocial profile of mothers and families post-diagnosis to assess what extent individuals' profiles match the collection of risk factors identified for each depressive symptom trajectory. The model has the potential to aid in predicting which trajectory might unfold and whether an intervention may be warranted. Recognizing that resources for mental health services are limited, priority for early intervention should be directed at mothers with increasing depressive symptoms in an effort to improve such an unfavorable trajectory. Our findings suggest there may be a window of opportunity to intervene on mothers' depressive symptoms to potentially interrupt unfavorable trajectories. Treating maternal depression has been shown to have immediate significant benefits. Recently in the health economics literature, Perry demonstrated that treatment of maternal depression resulted in a reduction of healthcare costs in the six months after having a child diagnosed with asthma.[45] This result supports health policy to invest in training

paediatric healthcare professionals to detect depressive symptoms in adults. Such a policy can lead to more efficient use of limited healthcare funds.

Being mindful of the mental and emotional state of caregivers is an important component of family-centered care, and may present an avenue for intervention that can potentially improve child outcomes.[46] It is a multidisciplinary model of healthcare delivery that may include, for example, physicians, nurses, psychologists, and social workers. Family-centered care has been shown to be associated with an increase in parents' satisfaction with healthcare services, lower parent stress, and with positive child health outcomes.[47] It is understandable how maternal depressive symptoms can become easily over-shadowed by a presenting child's epilepsy during the medical encounter. Healthcare professionals in this situation should be active in considering how the family environment influences the illness process and *vice versa*. The Bright Futures health promotion initiative encourages paediatric healthcare professionals to support families as part of providing care to children and recommends open questioning surrounding symptoms of maternal depression.[48, 49] It is a collaboration of the American Academy of Paediatrics and other institutional projects that provide resources for healthcare professionals guided by the principle that "every child deserves to be healthy and that optimal health involves a trusting relationship between the health professional, the child, the family, and the community" (http://www.brightfutures.org). There is value in more formally considering mothers' mental health during the clinic visit. Referrals to a social worker or local epilepsy support centers are resources that can be offered soon after diagnosis to help ensure the best possible outcomes for families.

This study has several strengths. First, to our knowledge this is the only study to prospectively document the course of depressive symptoms of mothers of children with epilepsy. In addition, the relatively large sample and strong response and retention rates increase the external validity of findings. Second, this study utilized the CES-D, a well-validated and reliable instrument to measure maternal depressive symptoms. Third, this study focused on incident rather than prevalent cases of

childhood epilepsy. Results may be useful for healthcare professionals as part of the initial consultation when diagnosing childhood epilepsy so as to prevent any potential negative impact of maternal depressive symptoms on child health outcomes.

This study also has some limitations. First, the sample under study was recruited from paediatric neurology practices that may not be representative of all families of a child with epilepsy, thus potentially limiting external validity. While it may be that some children are diagnosed and treated for new-onset epilepsy by a primary care paediatrician or family practitioner, it was not feasible to recruit a random sample of such physicians in a large national study. In the absence of population-based registries for epilepsy to facilitate such studies, Speechley et al. demonstrated that it may be feasible to recruit a representative population-based sample of children with epilepsy by targeting paediatric neurologists.[50] In this study, family physicians practicing in southwestern Ontario, reported they would refer between 80-99% of their patients with childhood epilepsy (depending on the type of seizure and syndrome) to a paediatric neurologist.

Second, it is important to consider that mothers with higher levels of depressive symptoms and other risk factors for clinical depression[51] were less likely to complete the 24-month follow-up compared to mothers who did not exhibit such traits. A similar trend has been observed in other research of mothers with depressive symptoms.[52, 53] Bias due to losses during follow-up may under-estimate the proportion of mothers at risk. When baseline characteristics of mothers who did not complete the study were compared to characteristics from each trajectory group, results showed that those lost during follow-up most closely resembled the *moderate increasing* group (i.e., younger, less likely to be married, lower socioeconomic status, and less favourable family environment). This means that the group of mothers classified as having what might be characterized as the most concerning pattern of depressive symptoms, that of *moderate increasing*, may actually be larger than estimated.

Third, since this study relied on mothers' perceptions of measures for both exposures and outcomes, there was potential for mothers' reports to be biased, threatening the study validity. This phenomenon, more commonly known as depression distortion,[54] was thoroughly investigated in a previous analysis using a series of regression analyses to determine if the association between mothers' and neurologists' reports of child health outcomes varied significantly when stratified by level of maternal depressive symptoms; results suggested no evidence of informant discrepancy in this sample of mothers.[55]

Conclusion

Risk for clinical depression is very common among mothers of children with new-onset epilepsy and decreases during the first 24 months of diagnosis. This research has demonstrated that mothers of children with new-onset epilepsy are not a homogeneous group of women with a single trajectory of change in depressive symptoms over time, but instead consist of distinct heterogeneous groups. Having a child with cognitive problems was the strongest risk factor in the model, significantly predicting those mothers who fell into the *moderate increasing* depressive symptoms trajectory group. It is important for healthcare professionals caring for children with epilepsy to be aware of how diagnosing epilepsy in a child can impact the mothers' mental health status. By adopting a family-centered approach, healthcare professionals may be able to alter trajectories of depressive symptoms in mothers to in turn promote more positive child outcomes.

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Table 4.1. Sample Baseline Characteristics of Mothers of Children with New-onset Epilepsy.*

	Study Sample	Completed Follow-up	Lost to Follow-up	t / χ^2	*P*-value
N	339	258	81		
Maternal Characteristics					
Age, years	37.7 (5.8)	38.4 (5.5)	35.6 (6.2)	3.73	0.0002
Marital Status, %					
Not Married	19.8	16.3	30.9	8.27	0.0040
Married†	80.2	83.7	69.1		
Employment Status, %					
Not Employed	9.5	7.8	15.2	5.26	0.1539
Employed	66.1	68.5	58.2		
Homemaker	22.9	22.6	24.1		
Student	1.5	1.2	2.5		
Education, %					
Primary School	11.5	8.5	21.0	10.91	0.0122
High School	20.9	20.2	23.5		
Technical Training	13.6	14.3	11.1		
College/University	54.0	57.0	44.4		
Number of Children	2.3 (0.9)	2.3 (0.9)	2.5 (1.0)	-1.67	0.0953
Depressive Symptoms, CES-D	14.6 (10.6)	13.8 (10.4)	17.0 (10.4)	-2.44	0.0152
Child Characteristics					
Age, years	7.4 (2.4)	7.5 (2.4)	7.4 (2.4)	0.23	0.8166
Sex, %					
Male	52.2	51.6	54.3	0.19	0.6632
Female	47.8	48.4	45.7		
Seizure Type, %					
Generalized	38.6	37.3	42.9	0.77	0.3808
Partial	61.4	62.7	57.1		

Quality of Life, QOLCE	70.4 (13.4)	71.1 (13.5)	68.2 (12.9)	1.64	0.1030
Epilepsy Severity, GASE	5.4 (1.2)	5.4 (1.1)	5.3 (1.3)	0.87	0.3845
Co-morbidities, %					
Behaviour Problems	14.1	13.3	16.5	2.46	0.4835
Cognitive Problems	13.6	10.2	24.3	12.41	0.0146
Motor Problems	6.3	5.9	7.8	0.95	0.6234
Family Characteristics					
Functioning, Family APGAR	14.0 (3.8)	14.1 (3.9)	13.4 (3.4)	1.54	0.1241
Resources, FIRM	50.1 (11.1)	50.9 (11.3)	47.6 (10.3)	2.33	0.0206
Demands, FILE	9.6 (6.5)	9.1 (6.2)	11.2 (7.4)	-2.34	0.0211
Perception of Patient-centered Care, PPPC	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	-0.17	0.8613
Annual Household Income, %					
< $20,000	7.7	5.7	14.3	13.50	0.0191
$20,000-39,999	13.5	12.1	18.2		
$40,000-59,999	21.2	22.6	16.9		
$60,000-79,999	18.2	16.5	23.4		
≥ $80,000	37.2	40.7	26.0		
Unknown	2.2	2.4	1.3		

*Reported as mean (standard deviation), unless otherwise stated.
†Includes those in married and common-law relationships.

Table 4.2. Parameter Estimates for the Four-group Trajectory Model of Depressive Symptoms in Mothers of Children with Epilepsy during the First 24 Months after Diagnosis.

Group	% Sample	Parameter	Estimate	Standard Error	*t*	*P*-value
1	59.3	Intercept	14.1	1.8	8.03	<0.0001
		Linear	-8.5	2.5	-3.38	0.0007
		Quadratic	2.8	1.0	2.76	0.0058
		Cubic	-0.3	0.1	-2.38	0.0173
2	25.1	Intercept	34.7	3.3	10.43	<0.0001
		Linear	-25.1	4.6	-5.48	<0.0001
		Quadratic	10.2	1.8	5.54	<0.0001
		Cubic	-1.2	0.2	-5.59	<0.0001
3	8.6	Intercept	32.1	1.8	17.43	<0.0001
		Linear	-9.9	1.5	-6.81	<0.0001
		Quadratic	2.0	0.2	8.36	<0.0001
4	7.1	Intercept	41.2	1.2	33.81	<0.0001
		Linear	-4.5	0.4	-12.61	<0.0001

Group 1 represents mothers with *low stable* depressive symptoms, Group 2 *borderline* symptoms, Group 3 *moderate increasing* symptoms, and Group 4 *high decreasing* symptoms.

Table 4.3. Maternal Depressive Symptoms over Time, Stratified by Trajectory Group.*

Measurement Occasion	Trajectory Group				*F*	*P*-value
	Low Stable	Borderline	Moderate Increasing	High Decreasing		
1 (baseline)	8.4 (5.5)	18.9 (6.6)	25.6 (7.8)	37.7 (7.1)	227.1	<0.0001†
2 (6 months)	6.2 (4.7)	16.5 (7.1)	21.8 (8.8)	31.1 (5.9)	162.5	<0.0001†
3 (12 months)	6.6 (4.7)	19.5 (7.7)	21.2 (8.7)	28.4 (10.7)	123.7	<0.0001†
4 (24 months)	7.2 (5.8)	15.7 (7.2)	34.4 (6.6)	18.1 (7.6)	132.1	<0.0001‡

*Reported as mean (standard deviation).

†No significant difference between *borderline* and *moderate increasing* groups.

‡No significant difference between *borderline* and *high decreasing* groups.

Table 4.4. Baseline Characteristics of Mothers of Children With New-onset Epilepsy, Stratified by Trajectory Group.*

	Trajectory Group						
	Low Stable	**Borderline**	**Moderate Increasing**	**High Decreasing**	***F* / χ^2**	***P*-value**	**Pairwise Contrasts**
Maternal Characteristics							
Age, years	38.7 (5.6)	37.1 (5.5)	34.2 (6.2)	35.7 (5.6)	6.99	0.0001	1 > 3
Married†, %	85.5	80.0	62.1	58.3	16.76	0.0008	1 > 3, 4 2 > 3, 4
Employed, %	67.3	73.5	44.8	54.2	9.52	0.0231	
College/University, %	63.0	45.9	41.4	20.8	21.25	<0.0001	1 > 2 – 4 2 > 4
Child Characteristics							
Age, years	7.6 (2.3)	7.2 (2.3)	7.0 (2.5)	7.9 (2.8)	1.04	0.3761	
Male, %	53.5	52.9	48.3	45.8	0.72	0.8886	
Partial Seizures, %	61.0	56.1	71.4	69.6	2.81	0.4212	
Quality of Life, QOLCE	73.6 (12.6)	68.4 (12.2)	65.7 (11.3)	56.4 (15.0)	14.86	<0.0001	1 > 2 - 4 2 > 4
Epilepsy Severity, GASE	5.5 (1.2)	5.3 (1.2)	5.2 (1.2)	5.3 (1.0)	0.69	0.5603	
Co-morbidities, %							
Behaviour Problems	10.1	18.3	20.7	26.1	7.65	0.0539	
Cognitive Problems	5.9	19.5	25.0	17.4	9.25	0.0262	
Motor Problems	4.5	9.8	10.7	4.4	3.78	0.2859	
Family Characteristics							
Functioning, Family APGAR	15.1 (3.2)	12.6 (3.3)	12.4 (4.1)	10.8 (5.3)	20.05	<0.0001	1 > 2 – 4
Resources, FIRM	54.6 (8.6)	44.8 (10.7)	43.9 (9.9)	38.8 (13.3)	37.74	<0.0001	1 > 2 – 4 2 > 4
Demands, FILE	7.9 (5.5)	10.3 (6.8)	14.4 (5.3)	14.9 (8.5)	17.44	<0.0001	1 < 2 – 4

							2 < 3, 4
Perception of Patient-centered Care, PPPC	1.5 (0.5)	1.7 (0.6)	1.4 (0.3)	1.7 (0.6)	2.56	0.0550	
Income ≥$80,000, %	40.3	38.3	20.7	26.1	5.75	0.1243	

*Reported as mean (standard deviation), unless otherwise stated.
†Includes those in married and common-law relationships.

Table 4.5. Multinomial Logistic Regression Identifying Baseline Predictors of Depressive Symptoms Trajectory Group Membership.*

	Trajectory Group			
	Low Stable†	**Borderline**	**Moderate Increasing**	**High Decreasing**
Maternal Age	1.00	0.53 (0.31, 0.94)	0.31 (0.12, 0.79)	0.64 (0.27, 1.52)
Maternal Education	1.00	0.88 (0.64, 1.20)	0.91 (0.53, 1.55)	0.38 (0.22, 0.65)
Child Quality of Life	1.00	0.90 (0.65, 1.23)	1.10 (0.63, 1.94)	0.42 (0.21, 0.84)
Child Cognitive Problems	1.00	2.00 (0.70, 5.71)	9.29 (2.01, 42.88)	0.56 (0.09, 3.54)
Family Functioning	1.00	0.65 (0.46, 0.90)	0.50 (0.28, 0.90)	0.64 (0.36, 1.16)
Family Resources	1.00	0.50 (0.35, 0.73)	0.72 (0.37, 1.41)	0.69 (0.34, 1.40)
Family Demands	1.00	0.91 (0.65, 1.30)	4.00 (1.72, 9.31)	2.00 (0.95, 4.21)

*Reported as odds ratio (95% confidence interval).
†Reference group.

Chapter Five

The Impact of Maternal Depressive Symptoms on Health-Related Quality of Life in Children with Epilepsy[a]

Introduction

Maternal depressive symptoms have been linked to a host of child health outcomes. Most commonly, children of mothers with depression are at a significantly higher risk for depression and behavior problems as compared to children of mothers without depression.[1, 2] In childhood epilepsy, few studies have specifically focused on the impact of maternal depressive symptoms on child health outcomes. Early work by Hoare and Hoare and Kerley demonstrated that psychiatric disturbances in mothers were associated with psychiatric problems in children.[3, 4] These results were verified by more recent work by Adewuya and Ola, which showed that psychiatric morbidity in parents was significantly associated with anxiety and depression in adolescents with epilepsy.[5] Two studies have examined the impact of maternal depressive symptoms on behavior problems in children with epilepsy and found a positive association between maternal depressive symptoms and child behavior problems.[6, 7] Three studies have assessed the impact of maternal depressive symptoms on child health-related quality of life revealing some support for a negative impact of maternal depressive symptoms on overall health-related quality of life in children with epilepsy.[7-9]

Our recent systematic review found that previous studies examining the impact of maternal depressive symptoms on child outcomes in epilepsy suggested a need for more methodologically robust research.[10] While studies generally reported a negative association between maternal depressive symptoms and child outcomes,

[a]A version of this section was published elsewhere as, Ferro MA, Avison WR, Campbell MK, Speechley KN. The impact of maternal depressive symptoms on health-related quality of life in children with epilepsy: a prospective study of family environment as mediators and moderators. Epilepsia 2011;52(2):316-25.

several limitations in study design including a lack of prospective cohort studies, inclusion of non-representative samples, and sampling procedures prone to selection bias make it difficult to reach definitive conclusions. Thus, there is a need to prospectively assess how maternal depressive symptoms may impact health-related quality of life in children newly-diagnosed with epilepsy.

The objectives of this research were to examine the impact of maternal depressive symptoms on health-related quality of life in children with new-onset epilepsy and to identify family factors that moderate and mediate this relationship during the first 24 months after epilepsy diagnosis. Given that previous work in this population has shown that, on average, child health-related quality of life improves during the first 24 months after diagnosis,[11] it was hypothesized that depressive symptoms in mothers would negatively impact children's health-related quality of life, such that children of mothers with elevated levels of depressive symptoms would have poorer health-related quality of life and less favourable rate of change during the 24-month follow-up. Also, it was hypothesized that the negative impact of maternal depressive symptoms on child health-related quality of life would be moderated by family resources and maternal perception of the healthcare received by her child. Finally, it was hypothesized that this relationship would be mediated by family functioning and family demands such that elevated levels of depressive symptoms would lead to worse family functioning and more family demands, resulting in poorer child health-related quality of life during follow-up.

Methods

Sample and Data Source

Data for this study came from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES), a prospective cohort study designed to examine the determinants of health-related quality of life in children with epilepsy during the first 24 months post-diagnosis. Participants were recruited primarily from

paediatric tertiary-care neurology practices across Canada, with a minority recruited from community-based paediatric neurology practices. The inclusion criteria for patients were as follows: 1) new case of epilepsy (≥2 unprovoked seizures), in whom diagnosis of epilepsy has not been previously confirmed, seen for the first time by a participating paediatric neurologist within the data collection period; 2) epilepsy diagnosed between the ages of 4-12 years; and, 3) parent must have been primarily responsible for the child's care for ≥6 months and continue to be for the duration of the study. Children with newly-diagnosed epilepsy with a prior history of neonatal seizures were included if medication was removed by six weeks of age without recurrence. Patients were excluded from the study if: 1) diagnosis of epilepsy had been previously confirmed by another physician; 2) diagnosed with other progressive or degenerative neurological disorder (e.g., mental retardation); 3) diagnosed with other major co-morbid non-neurological disorders that would have an impact on quality of life (e.g. asthma requiring daily medication, renal failure); and, 4) parent had insufficient English language skills to complete questionnaires.

In the absence of population-based registries for epilepsy to facilitate such studies, Speechley et al. demonstrated that it may be feasible to recruit a representative population-based sample of children with epilepsy by targeting paediatric neurologists.[12] In this study, family physicians practicing in southwestern Ontario, reported they would refer between 80-99% of their patients with childhood epilepsy (depending on the type of seizure and syndrome) to a paediatric neurologist. Primary caregivers were contacted by telephone to determine participation status and mailed questionnaires for self-administration after diagnosis (baseline), and at six, 12, and 24 months. A modified version of the Tailored Design Method was used to develop a structured follow-up strategy to enhance retention rates.[13] Of the 456 eligible families approached to participate, 443 (97.1%) verbally consented. Of these, 374 (83.7%) completed the baseline survey. For this analysis, only surveys completed by a child's mother (i.e., biological, adoptive, foster) were retained and used in the analysis 339 (91.0%). Approval for

HERQULES was obtained from all relevant research ethics boards across the country and parents provided written consent.

Measures

Child health-related quality of life

Child health-related quality of life was reported by mothers using the Quality of Life in Childhood Epilepsy (QOLCE).[14] The QOLCE is a multifaceted, parent-report, epilepsy-specific instrument for evaluating health-related quality of life of children with epilepsy aged 4-18 years. The QOLCE contains 76 items with 16 subscales spanning seven domains of life function including, physical activities, social activities, cognition, well-being, behavior, general health, and general quality of life.[14] Items are rated on a five-point Likert scale, which are used to calculate the 16 subscale scores ranging from zero (low functioning) to 100 (high functioning). The subscale scores are averaged to produce an overall health-related quality of life score. It has demonstrated good construct validity, internal consistency reliability, and sensitivity to epilepsy severity.[15] The internal consistency reliabilities were excellent for all measurement occasions in this sample (0.92-0.94).

Epilepsy Characteristics

Neurologists completed a questionnaire documenting the clinical factors of each child's epilepsy including: severity of epilepsy, seizure type and frequency, type of epilepsy syndrome, age at onset and diagnosis, medication information, and adverse effects. Neurologists were also asked to rate the presence of comorbidities using single-item measures, specifically, any behavior (0=none to 3=severe), cognitive (0=none to 4=severe), or motor problems (0=none to 3=severe). Severity of epilepsy was classified using the Global Assessment of Severity of Epilepsy (GASE), a single-item measure developed for HERQULES.[16] Using the GASE, neurologists rate the overall severity of each child's epilepsy using a seven-point scale ranging from

1=extremely severe to 7=not at all severe. The GASE has demonstrated minimum burden on participants, adequate content, convergent, and construct validity, and high intra- and inter-rater reliability.[16]

Maternal Depressive Symptoms

Level of depressive symptoms in mothers was measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item questionnaire designed to assess depressive symptoms over the past week.[17] The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. A four-point Likert scale (0-3) is used to rate the frequency of symptoms experienced. The total score spans from 0-60, with a higher score indicating greater impairment. Individuals with a total score of ≥16 are typically identified as being at risk for clinical depression. In this sample, internal consistency estimates were good, ranging from 0.75-0.80.

Family Environment

Three aspects of the family environment (functioning, resources, and demands) were measured based on parent-report. The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR) was used to assess satisfaction with family relationships.[18] The Family APGAR is a five-item instrument where responses are based on a five-point Likert scale, ranging from 0-4 for each item. Higher scores indicate higher satisfaction with family functioning. The Family APGAR has been found to be valid and reliable in both the clinical and research setting with adults and children.[18-20] The internal consistency reliabilities in this sample were very good, with Cronbach's α ranging from 0.86-0.89.

The Family Inventory of Resources for Management (FIRM) was utilized to assess resources available to aid families' adaptation to stressful events.[21] For this study, only two subscales (family mastery and health, extended family social support)

which have been found to be associated with adaptation to childhood epilepsy were used.[22] Scoring procedures for the FIRM involve summing all response values, which range from 0 (not at all) to 3 (very well) to provide a total FIRM score. The FIRM has demonstrated adequate reliability and validity properties.[21] Internal consistency reliabilities in this sample ranged from 0.91-0.93 for the Family Mastery and Health subscale and 0.44-0.54 for the Extended Family Social Support subscale.

Family demands were quantified using the Family Inventory of Life Events and Changes (FILE), which assesses the pile-up of simultaneous normal and non-normal life events and changes in life events experienced by a family during the previous year.[23] There are 71 items in the FILE with the score computed by giving each "yes" response a score of one. Summing responses provides a score for each subscale and the total pile-up score. The reliability and validity of the FILE is well-established.[23] As measured by Cronbach's α, the overall reliability of the FILE was excellent, ranging from 0.98-0.99 in this sample.

Socio-demographic information was also collected including date of birth (mother and child), child gender, number of children in household, parents' marital and employment status, highest level of completed education, and total annual household income.

Perception of Patient-centered Care

Based on the Patient-Centered Model of Care, a modified version of the Patient Perception of Patient-centeredness (PPPC) was used to assess mothers' perceptions of the extent to which the healthcare services her child received were patient-centered.[24] Seven of the original 14 items were slightly modified to make them appropriate for parent-report by replacing "your" with "your child's" and "you" with "your child". The PPPC is scored so that low scores correspond to positive perceptions. Inter-item reliability has been found to be adequate for the PPPC and validity was established through a significant correlation with the Measure of

Patient-centered Communication.[25] In this sample, the internal consistencies were good, ranging from 0.77-0.86.

Statistical Analysis

Univariable analyses used to describe maternal depressive symptoms at baseline included descriptive statistics and frequency distributions. Individual growth curve modeling was used to examine the impact of maternal depressive symptoms on child health-related quality of life during the 24-month follow-up.[26] Such an approach can handle designs with repeated measures. The models were built following the guidelines suggested by Singer.[27] In particular, time since child was diagnosed with epilepsy and maternal depressive symptoms as time-varying predictors of child health-related quality of life. Both the model intercept and slope were specified as random effects (i.e., differing for each individual in the sample). An unstructured variance-covariance matrix was specified, which is the most heterogeneous type and requires estimation of several parameters, thus additional degrees of freedom, but does not constrain any pairwise comparisons within the matrix, allowing for additional flexibility.[28] Variables were centered on their respective sample means at 24 months to improve interpretation of results.

Potential confounders were tested *a priori* to the growth curve modeling. The variables tested were child age, child sex, epilepsy severity, seizure type, age of onset, severity of co-morbidities, anti-epileptic drug use, maternal age, education, employment status, parity, marital status, and family income. Confounding was determined by adding the variable to the model to examine the change in the effect estimate. For the purposes of this study, a collapsibility criterion was used to operationally define confounders as those variables, when entered in the model resulted in a ≥10% change in the effect estimate of maternal depressive symptoms on child health-related quality of life.[29]

Moderation was examined by sequentially testing growth curve models of child health-related quality of life regressed on maternal depressive symptoms in the presence of each potential moderator using a product interaction term.[30] To examine whether family resources or perception of patient-centered care moderated the impact of maternal depressive symptoms on child health-related quality of life at the 24-month follow-up, a two-way interaction between maternal depressive symptoms and the moderator was entered in the model. A three-way interaction between maternal depressive symptoms, the moderator, and time was entered to examine whether the magnitude of the moderating effect varied over time. The moderation analyses conformed to Kleinbaum's Hierarchy Principle such that maternal depressive symptoms and moderator main effects were included in the model assessing the interaction term.[31]

The product of coefficients method described by MacKinnon et al. was used to examine the potential mediating effects of family functioning and family demands on the relationship between maternal depressive symptoms and child health-related quality of life as illustrated in Figure 5.1.[32] The product of coefficients method has been shown to have more accurate type I error rates and greater statistical power compared to the more traditionally employed causal steps described by Baron and Kenny.[33] Instead the product of coefficients approach involved estimating two growth curve models and computing the product of $\hat{\alpha}$ and $\hat{\beta}$ to form the mediated or indirect effect.

$$M = c_M + \alpha X + \varepsilon_M$$

$$Y = c_Y + \tau X + \beta M + \varepsilon_Y$$

The rationale behind this approach is that mediation is dependent upon the extent to which the predictor impacts the mediator, α, and the extent to which the mediator impacts the outcome, β. The proportion of the total effect that is mediated

was calculated using a ratio of the indirect effect, $\widehat{\alpha\beta}$, divided by the total effect, $\widehat{\alpha\beta} + \hat{\tau}$. Significance of the mediated effect was tested by dividing the product by its standard error and compared to the standard normal distribution and by construction of confidence intervals. The standard error of $\widehat{\alpha\beta}$ was calculated using the method described by Sobel.[34] The Sobel method is the most commonly used approach to calculating the standard error and has been shown to produce unbiased and statistically robust results.[32] Growth curve models used in the mediation analysis were adjusted for potential confounding factors using the methods described by Li et al. in order to obtain unbiased estimates of effect.[35] Data analysis was conducted with Statistical Analysis Software (SAS 9.1.3 Service Pack 4, SAS Institute Inc., Cary, NC). All hypothesis tests were two-sided with α=0.05.

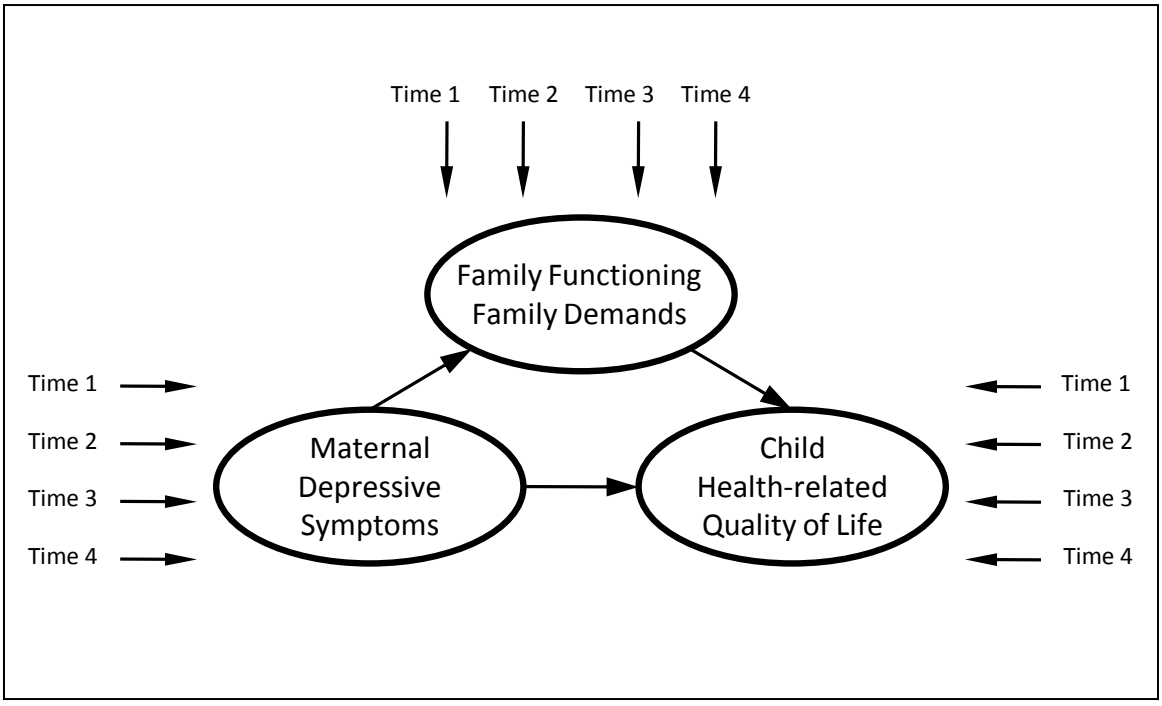

Figure 5.1. Hypothesis of the Mediational Relationship between Maternal Depressive Symptoms and Child Health-related Quality of Life. The illustration represents a dynamic model that incorporates prospective measurements on each variable during the 24-month follow-up.

Missing Data

Handling missing data for children's health-related quality of life followed the strategy described by Wirrell et al.[36] Briefly, if less than 20% of subscores in the QOLCE were missing, the child's health-related quality of life score was calculated by determining the mean for the other subscales, and applying that mean value for the missing subscale(s). If more than 20% of subscales were missing, that participant was excluded from analysis. The number of participants for whom missing data prevented calculation of a QOLCE score was not systematic over the 24-month follow-up (n=28, n=28, n=24, and n=15 for baseline, and 6, 12, and 24 months, respectively). Because of the extensive use of covariates in the models examined in this study, it was assumed that the probability of "missingness" was not dependent on any unobserved data and thus, the data did not violate the requirements for data that are missing at random. This is a required assumption for growth curve modeling using PROC MIXED. Participants with at least one measurement occasion were included in the analysis.

Results

Sample Characteristics

A total of 339 mothers were included in the study. Mothers had a mean age of 37.7 (standard deviation 5.8) years at baseline. Approximately half of the children were male (52.2%). Children had a mean age of seizure onset of 6.9 (2.5) years and a mean age of 7.4 (2.4) years at baseline. Children had a mean score of 70.4 (13.4) on the QOLCE and the majority of children (58.7%) had "a little severe" or "somewhat severe" epilepsy using the GASE score. Mean scores on family environment measures were as follows: Family APGAR, 14.0 (3.8); FIRM 50.1 (11.1); and, FILE 9.6 (6.5) indicating that families were functioning well, had adequate resources and relatively few demands on them. Additional baseline and 24-month characteristics of the study sample are shown in Table 5.1. At baseline, 38% of mothers scored

above the cut-point for risk of depression (i.e., CES-D ≥16). This proportion decreased to 30% at 24 months.

Impact of Maternal Depressive Symptoms on Child Health-related Quality of Life

Growth curve models for changes in child health-related quality of life over time are shown in Table 5.2. Potential confounders were tested *a priori* to fitting the growth curve models and none met the criterion for inclusion, thus in the interest of model parsimony, unadjusted models are presented. There was significant improvement in model fit between each step in the modeling strategy (χ^2=86.3, *df*=1, *p*<0.0001; χ^2=114.5, *df*=2, *p*<0.0001). In the first model, a mean score of 73.1 on the QOLCE was observed for the unconditional means model which assumes static health-related quality of life over time. The unconditional growth curve model, which includes a linear function of time, shows that QOLCE scores increase significantly during the 24-month follow-up (β=1.17, *p*<0.0001). The final model includes mothers' CES-D scores in predicting child QOLCE scores over time. Maternal depressive symptoms were observed to have a negative impact on both QOLCE scores at 24 months (β=-0.47, *p*<0.0001) and on the rate of change in QOLCE scores during follow-up (β=-0.04, *p*<0.0250).

Results from each model suggest a need for additional time-varying and time-invariant predictors of child health-related quality of life, given by the significant amount of residual variation in the intra- and inter-individual components of the growth curve models (Table 5.2). Interestingly, there was significant covariance observed between the intercept and slope in the growth curve models, indicating that children with higher QOLCE scores also had greater rates of change over time. Trajectories for mothers with high and low CES-D scores based on results from the conditional growth curve model are illustrated in Figure 5.2.

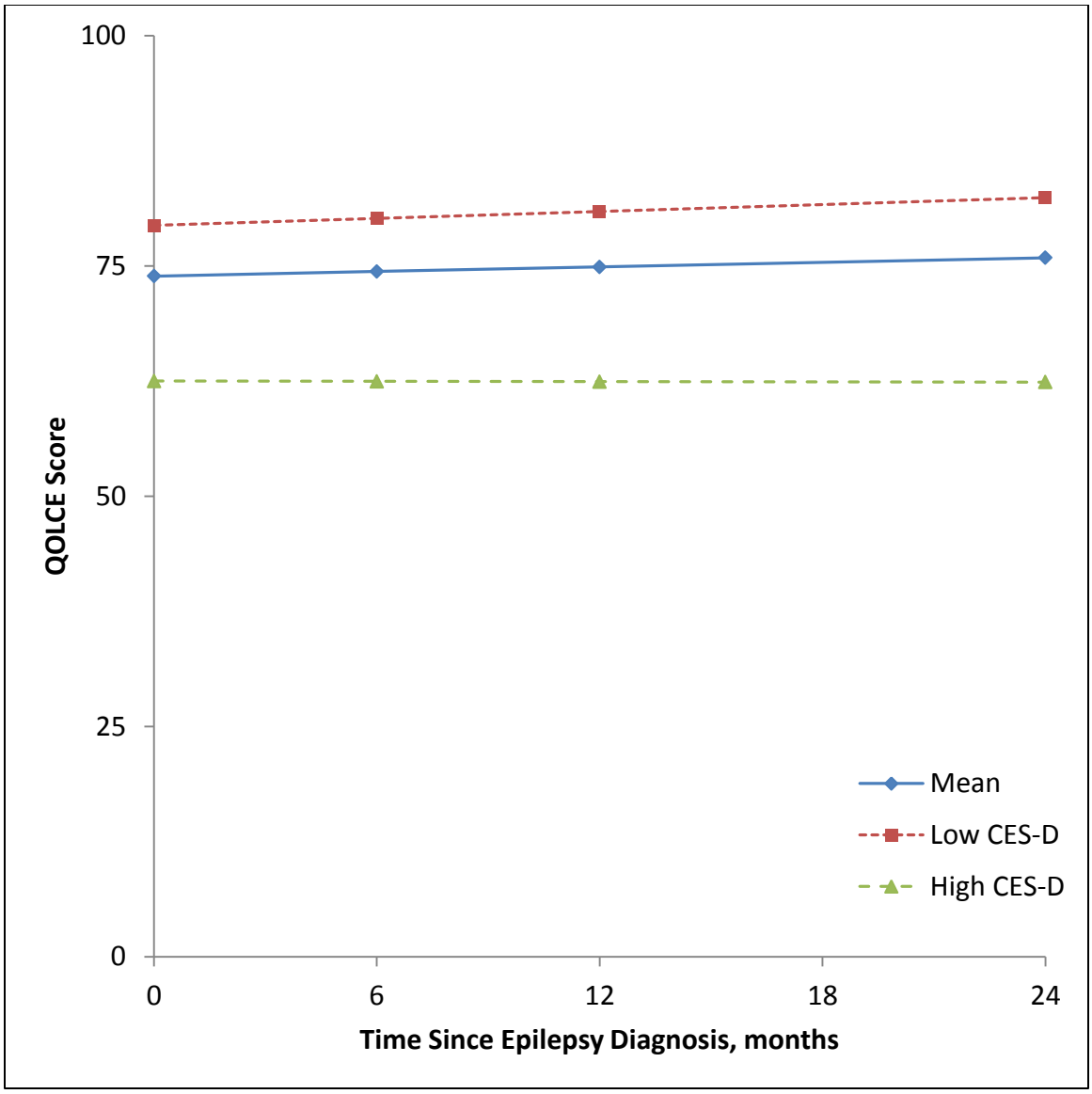

Figure 5.2. Change in Child Health-related Quality of Life over 24 Months. Child health-related quality of life was measured using the Quality of Life in Childhood Epilepsy (QOLCE). The solid line represents the trajectory for children of average mothers; the dotted line represents the trajectory for children of mothers with a Center for Epidemiological Studies Depression Scale (CES-D) score in the bottom 5%; and, the dashed line represents the trajectory for children of mothers with a CES-D score in the top 5%.

Moderating Effects of Family Resources and Perception of Patient-centered Care

The potential moderating effects of family resources and perception of patient-centered care were examined by including an interaction term between mothers'

CES-D scores and the moderator in the growth curve model. Results from the two models are shown in Table 5.3. Family resources moderated the impact of maternal depressive symptoms on child health-related quality of life (β=0.25, p<0.0243) and the magnitude of the moderating effect varied over time (β=0.09, p<0.0212). This moderating effect is illustrated in Figure 5.3. In contrast, perception of patient-centered care was not observed to significantly moderate the relationship between maternal depressive symptoms and child health-related quality of life (β=3.48, p=0.1281).

Mediating Effects of Family Functioning and Family Demands

The product of coefficients method was used to examine the potential mediating effects of family functioning and family demands in two sets of growth curve models during the 24-month follow-up. Results from the mediation analyses are shown in Table 5.4. Family functioning was observed to partially mediate the impact of maternal depressive symptoms on child health-related quality of life ($\widehat{\alpha\beta}$=-0.07, p=0.0007). The proportion of the total effect of maternal depressive symptoms on child health-related quality of life mediated by family functioning was 20%. In comparison, family demands were also observed to partially mediate this relationship ($\widehat{\alpha\beta}$=-0.12, p=0.0006). The proportion of the total effect mediated by family demands was 29%.

In a *post hoc* analysis examining the mediating effect of family functioning and family demands simultaneously in a two-mediator model, the proportion of total effect mediated was 45% ($\widehat{\alpha\beta}$=-0.19, p<0.0001). There was no significant difference between the family functioning- and family demands-specific effects ($\Delta\widehat{\alpha\beta}$=0.05, p<0.8708).

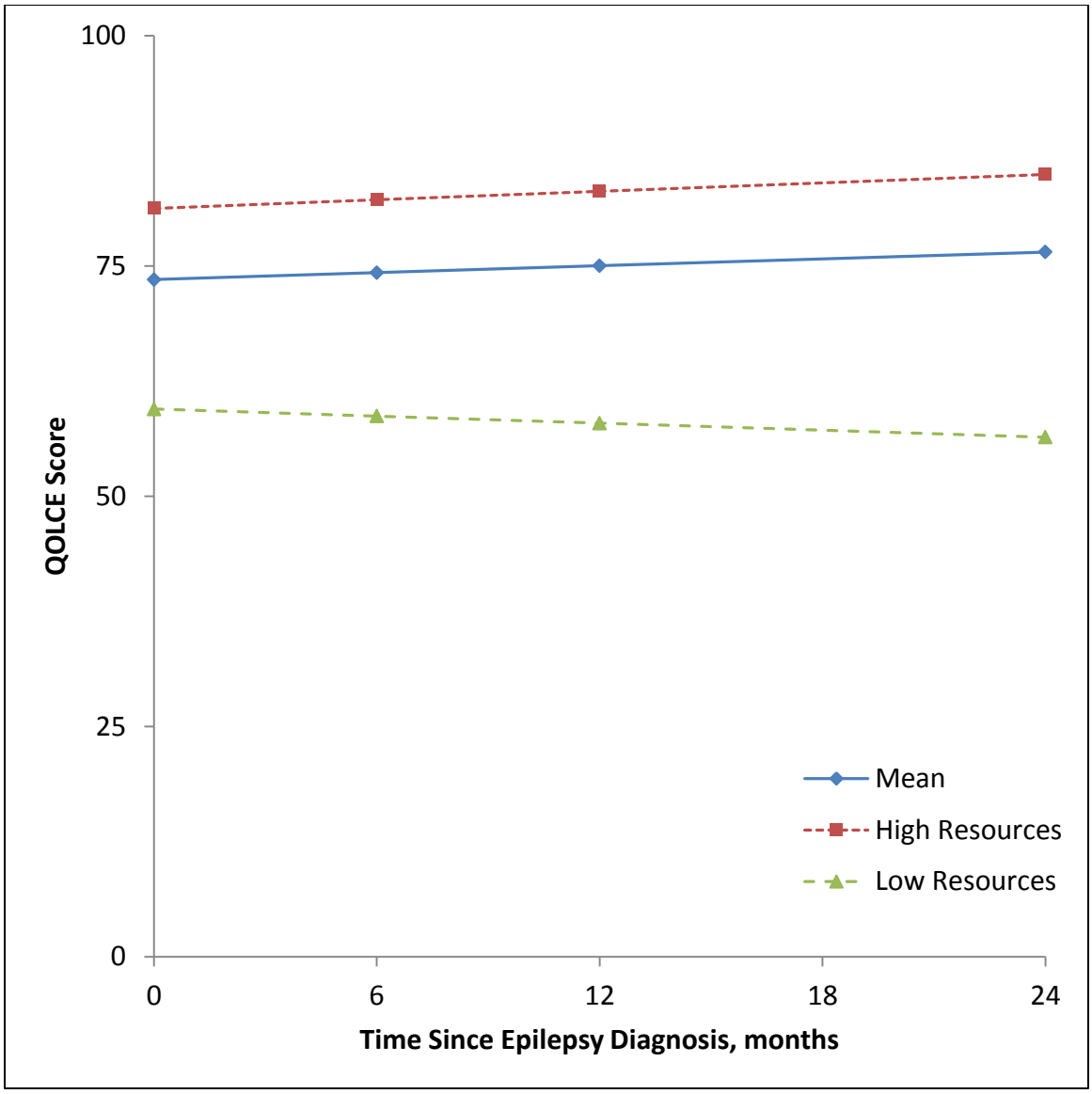

Figure 5.3. Moderating Effect of Family Resources on the Relationship between Maternal Depressive Symptoms and Child Health-related Quality of Life over 24 Months. Child health-related quality of life was measured using the Quality of Life in Childhood Epilepsy (QOLCE).The solid line represents the trajectory for children with mothers with average levels of depressive symptoms and average family resources; the dotted line represents the trajectory for children with mothers with average levels of depressive symptoms and in the bottom 5% for family resources; and, the dashed line represents the trajectory for children with mothers with average levels of depressive symptoms and in the top 5% for family resources.

Discussion

Based on self-reported screening results, pproximately one-third of mothers of children with new-onset epilepsy are at risk for clinical depression. This proportion is much higher compared to mothers in the general population, where previous research suggests that about 17% are considered at risk for depression.[37] When assessed over the first 24 months after diagnosis of epilepsy, maternal depressive symptoms appeared to have a significant negative impact on child health-related quality of life. This result is consistent with previous estimates from cross-sectional studies that included samples of children with more established epilepsy.[7-9] However, none of these studies focused specifically on mothers of children with new-onset epilepsy and none followed participants prospectively over time. Not only do children of mothers with elevated levels of depressive symptoms have poorer health-related quality of life compared to mothers with low levels of depressive symptoms, but their rate of change is also significantly less favourable during the first 24 months after diagnosis. Whereas children of mothers with lower levels of depressive symptoms have improved health-related quality of life scores over time, children of mothers with elevated symptoms show no evidence of improvement.

Results from this study also demonstrated that family resources, but not perception of patient-centered care, moderated the impact of maternal depressive symptoms on child health-related quality of life. Children of mothers experiencing depressive symptoms, but having more family resources, including social support systems, had significantly improved health-related quality of life during the first 24 months after diagnosis, compared to child of mothers with fewer family resources. The children in this latter group actually experienced declines in their health-related quality of life over time. The moderating effect of family resources on the relationship between maternal depressive symptoms and child health outcomes in epilepsy has been observed in previous cross-sectional studies. Baum et al. reported that family resources moderated the relationships between temperament and internalizing and

externalizing behavior problems in children with epilepsy[38] and Fastenau et al. noted a moderating effect of family resources on children's academic achievement.[39] Interestingly, the magnitude of the moderating effect of family resources on maternal depressive symptoms on child health-related quality of life varied significantly over time. Larger effects were observed at later measurement occasions during the 24-month follow-up. This is consistent with the Convoy Model proposed by Kahn and Antonucci.[40] The Convoy Model offers a framework within which to understand how an assembly of family and friends are available as resources to an individual in times of need. Convoys are dynamic across time and situations whereby each life change brings with it the potential to reconstitute the convoy as the individual seeks to construct a network of resources that meets her support needs.[41] In this sample, mothers may observe improvement in their child's health-related quality of life with the addition of supportive resources, which may in turn lead mothers to acquire additional resources, resulting in further improvements in child health-related quality of life over time. Thus, it appears that the accumulation of resources is the driving force for the dynamic moderating effect observed over time. The fact that perception of patient-centered care did not moderate the impact of maternal depressive symptoms on child health-related quality of life was unlikely to be the result of missing important effects since the study was adequately powered to detect statistically significant interactions, as described by McCarthy.[42]

In addition, the study demonstrated that family functioning and family demands partially mediated the impact of maternal depressive symptoms on child health-related quality of life during the 24-month follow-up. This result is consistent with previous research which has shown that current and past depressive symptoms in mothers are significant predictors of lower family functioning[43] and that family functioning (as measured by parental behavior), mediates the relationship between maternal depression and child health outcomes in both healthy and chronically ill paediatric populations.[44-46] Elgar et al. showed that the quality of the child's rearing environment mediated the impact of maternal depressive symptoms on child and

adolescent maladjustment over a two-year period.[45] In comparison, Lim et al. showed that parenting quality partially mediated the relationship between maternal depression and child internalizing behavior problems.[46]

Being mindful of the mental state of caregivers and the climate of the family environment is an important component of family-centered care, and may present avenues for intervention that can potentially improve child outcomes.[47] Family-centered care has been shown to be associated with an increase in parents' satisfaction with healthcare services, lower parent stress, and with positive child health outcomes.[48] Detection and treatment of maternal depression have been shown to have immediate significant benefits. Recently in the health economics literature, Perry demonstrated that treatment of maternal depression resulted in a reduction of healthcare costs in the six months after having a child diagnosed with asthma.[49] This result supports health policy to invest in training paediatric healthcare professionals to detect depressive symptoms in adults. Such a policy can lead to more efficient use of limited healthcare funds.

This study has several strengths. First, to our knowledge this is the only study to prospectively document the depressive symptoms of mothers of children with epilepsy. In addition, the relatively large sample and strong response and retention rates increase the external validity of findings. Second, this study utilized the CES-D, a well-validated and reliable instrument to measure maternal depressive symptoms. Third, the potential for bias in mothers' reports associated with depression distortion,[50] was investigated in this study and no evidence of informant discrepancy was found in this sample of mothers.[51] If it was the case that depressed mothers' reports were negatively biased, this bias should be detected by comparing mothers' and neurologists' reports of children's health-related quality of life. That is, the association between mothers' and neurologists' reports would vary significantly when stratified by level of maternal depressive symptoms, if mothers' reports are biased by symptoms of depression. Interactions, depicted as product terms between CES-D scores and neurologist-reported measures, were used to determine the

presence of depression distortion. There was a lack of evidence to support depression distortion in this sample.[51] Fourth, this study focused on incident rather than prevalent cases of childhood epilepsy. Results may be useful for healthcare professionals as part of the initial consultation when diagnosing childhood epilepsy so as to prevent any potential negative impact of maternal depressive symptoms on child health outcomes.

Results from this study are tempered by a few limitations. First, the fact that mothers with higher levels of depressive symptoms and other risk factors for clinical depression were less likely to complete the 24-month follow-up compared to mothers who did not exhibit such traits.[52] A similar trend has been observed in other research of mothers with depressive symptoms.[53, 54] Bias due to losses during follow-up may under-estimate the proportion of mothers at risk and limit the external validity of results. Second, although there was no evidence to suggest that mothers were not valid informants, concerns regarding the accuracy and acceptability of parent-proxy ratings of children's health-related quality of life continue to be raised, because research has shown that children and parents do not necessarily share similar views about illness.[55] While not feasible in the current study, the young patient's perspective on the experience with illness should also be incorporated in future investigations. Third, this sample may not be completely representative of the Canadian population.[56] Compared to women in the general population, this sample of mothers had a larger proportion with a college or university education (54.5% vs. 45.9%), income ≥$80,000 (37.2% vs. 28.3%), and married (80.2% vs. 46.4%). The fact that this sample had a larger proportion of married women compared to the general population was expected since this study focused on mothers of children with epilepsy.

Conclusion

The negative impact of maternal depressive symptoms on health-related quality of life in children with new-onset epilepsy is significant during the first 24 months of

diagnosis. This research has demonstrated that children of mothers with elevated levels of depressive symptoms have poorer health-related quality of life over time and this relationship is moderated by family resources and partially mediated by family functioning and family demands. It is important for healthcare professionals caring for children with epilepsy to be aware of how diagnosing epilepsy in a child can impact the mothers' mental health status and the family environment. By adopting a family-centered approach, healthcare professionals may be able to intervene at the maternal or family level to in turn promote more positive outcomes in children with epilepsy.

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Table 5.1. Description of Maternal, Child, and Family Characteristics.

	Baseline N=339	24 Months N=258
Maternal Characteristics		
Age, years	37.7 (5.8)	40.4 (5.5)
Marital Status, %		
Not Married	19.8	18.1
Married*	80.2	81.9
Employment Status, %		
Not Employed	9.5	6.6
Employed	66.1	77.7
Homemaker	22.9	15.2
Student	1.5	0.4
Education, %		
Primary School	11.5	5.0
High School	20.9	19.2
Technical Training	13.6	11.9
College/University	54.0	63.9
Number of Children	2.3 (0.9)	2.3 (0.9)
Depressive Symptoms, CES-D	14.6 (10.6)	12.0 (10.0)
Child Characteristics		
Age, years	7.4 (2.4)	9.4 (2.4)
Age at Onset, years	6.9 (2.5)	6.8 (2.5)
Sex, %		
Male	52.2	51.6
Female	47.8	48.4
Seizure Type, %		
Generalized	38.6	37.3
Partial	61.4	62.7
Anti-epileptic Drugs, %	68.2	76.8
Health-related Quality of Life, QOLCE	70.4 (13.4)	75.9 (13.9)
Epilepsy Severity, GASE	5.4 (1.2)	6.3 (1.0)
Co-morbidities, %		
Behavior Problems	14.1	20.0
Cognitive Problems	13.6	17.5
Motor Problems	6.3	5.7
Family Characteristics		
Functioning, Family APGAR	14.0 (3.8)	14.1 (3.8)
Resources, FIRM	50.1 (11.1)	50.7 (11.5)
Demands, FILE	9.6 (6.5)	7.9 (5.8)
Perception of Patient-centered Care, PPPC	1.6 (0.5)	1.6 (0.6)
Annual Household Income, %		
< $20,000	7.7	4.0

$20,000-39,999	13.5	10.0
$40,000-59,999	21.2	18.8
$60,000-79,999	18.2	18.4
≥ $80,000	37.2	44.0
Unknown	2.2	4.8

Reported as mean (standard deviation), unless otherwise stated.
*Includes mothers in married and common-law relationships.

Table 5.2. Growth Models for the Impact of Maternal Depressive Symptoms on Child Health-related Quality of Life.

	Model A	Model B	Model C
Fixed Effects			
Final Status			
Intercept	73.14 (0.67)*	76.09 (0.85)*	75.88 (0.72)*
CES-D			-0.47 (0.06)*
Rate of Change			
Time		1.17 (0.19)*	0.99 (0.15)*
CES-D × Time			-0.04 (0.02)§
Variance Components			
Level 1			
Intra-individual	56.26 (2.88)*	41.32 (2.62)*	41.89 (2.70)*
Level 2			
Final Status	129.31 (11.74)*	166.62 (17.86)*	133.99 (15.64)*
Linear		4.22 (0.90)*	2.79 (0.82)†
Covariance		12.36 (3.22)†	8.95 (2.90)‡
Goodness-of-Fit			
Deviance	8224.5	8138.2	8023.7

Values denote β-coefficient (standard error). Model A is the unconditional means model; Model B is the unconditional growth model; Model C is the growth model conditional on maternal depressive symptoms.

*p<0.0001, †p<0.001, ‡p<0.01, §p<0.05

Table 5.3. Moderating Effects on the Relationship between Maternal Depressive Symptoms on Child Health-related Quality of Life.

	Estimate	Standard Error	*P*-value
Model A			
Final Status			
Intercept	77.05	0.81	<0.0001
CES-D	-1.43	1.38	0.3016
Family Resources	0.41	0.06	<0.0001
CES-D × Family Resources	0.25	0.11	0.0243
Rate of Change			
Time	1.43	0.20	<0.0001
CES-D × Time	0.18	0.46	0.6976
Family Resources × Time	0.02	0.02	0.2565
CES-D × Family Resources × Time	0.09	0.04	0.0212
Model B			
Final Status			
Intercept	76.19	0.85	<0.0001
CES-D	-5.62	1.32	<0.0001
Perception of Patient-centered Care	-2.00	1.19	0.0933
CES-D × Perception of Patient-centered Care	3.48	2.28	0.1281
Rate of Change			
Time	1.30	0.20	<0.0001
CES-D × Time	-0.57	0.45	0.1983
Perception of Patient-centered Care × Time	0.01	0.39	0.9758
CES-D × Perception of Patient-centered Care × Time	1.52	0.84	0.0710

Model A includes family resources as the moderating variable and Model B includes perception of patient-centered care as the moderating variable.

Table 5.4. Mediating Effects on the Relationship between Maternal Depressive Symptoms on Child Health-related Quality of Life.

	Equation 1	Equation 2	$\widehat{\alpha\beta}$	95% CI	*Z*-value	*P*-value
Mediator: Family Functioning						
Intercept	76.20 (0.76)*	14.00 (0.20)*	-0.07	-0.11, -0.03	3.39	0.0007
Time	1.08 (0.18)*	-0.02 (0.05)‡				
CES-D	-0.30 (0.06)*	-0.11 (0.01)*				
Family APGAR	0.64 (0.17)†					
Mediator: Family Demands						
Intercept	76.14 (0.77)*	7.98 (0.28)*	-0.12	-0.19, -0.05	3.44	0.0006
Time	1.09 (0.19)*	-0.25 (0.08)†				
CES-D	-0.29 (0.07)*	0.27 (0.02)*				
FILE	-0.45 (0.12)†					

Values denote β-coefficient (standard error).
CI, confidence interval.
*p<0.0001, †p<0.001, ‡not significant

Chapter Six

General Discussion and Conclusions

Introduction

This chapter summarizes the results and implications of the study, discusses the broader strengths and limitations of the work, and provides future research directions.

The purpose of this study was to 1) estimate the prevalence and course of depressive symptoms over 24 months among mothers of children with new-onset epilepsy; 2) identify subgroups of mothers with similar trajectories of depressive symptoms; and, 3) assess the family factors involved in the causal pathway between maternal depressive symptoms and child health-related quality of life over 24 months. As well, the question of whether depressive symptoms affect the validity of mothers' reports of child health-related quality of life was examined. Data were obtained from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES).

Research evidence reviewed in Chapter Two suggested that approximately one-third of mothers of children with epilepsy experience elevated levels of depressive symptoms and that maternal, child, and family factors predict risk for clinical depression. In addition, previous research suggested a negative relationship between maternal depressive symptoms and child outcomes, particularly health-related quality of life. Access to a sample of mothers of children newly-diagnosed with epilepsy provided a unique opportunity to study these relationships in this population. This was of interest given that epilepsy is the most common neurological condition affecting children and that the clinical management of epilepsy is dynamic during the first year after diagnosis.[1, 2] Also, given that mothers

are most often the primary caregivers for children, it is important to better understand mothers' mental health status during this time.

Summary of Results

Sample Characteristics

This study had a good initial response rate and high rate of retention. Over 300 mothers participated. Mothers who were lost to follow-up during the study were more likely to be younger, not married, less educated, have lower household income, and more likely to have a child rated by his/her neurologist as having cognitive problems at baseline compared to mothers who remained in the study. In addition, those who were lost to follow-up had more depressive symptoms, fewer family resources, and more family demands at baseline compared to those mothers who completed the study.

Mothers were approximately 40 years of age at baseline and the majority were married, employed, and had college/university education. Maternal depressive symptoms were measured using the 20-item Center for Epidemiological Studies Depression Scale (CES-D).[3] Across all measurement occasions mothers' mean CES-D score was slightly below the cut-off for being at risk for clinical depression (CES-D ≥16).

Approximately half of the children in the study were male. Children were approximately seven years of age at baseline. The majority of children had partial seizures. As measured by the Quality of Life in Childhood Epilepsy (QOLCE)[4] and Global Assessment of Severity of Epilepsy (GASE),[5] children had relatively good health-related quality of life and benign epilepsy.

Results from measures of family environment [Family Adaptability, Partnership, Growth, Affection, Resolve (Family APGAR),[6] Family Inventory of Life Events and

Changes (FILE),[7] Family Inventory of Resources for Management (FIRM)[8]] describe families that were, on average, functioning well, had low stress, adequate resources, and high socio-economic status.

Depressive Symptoms as Moderating Maternal Reports

Mothers with elevated depressive symptoms were not observed to provide biased reports of their child's health-related quality of life. That is, as neurologists reported higher scores on health-related quality of life outcomes, so did mothers, regardless of their mental health status. This suggested that mothers were valid informants for reporting on outcomes pertaining to their child with epilepsy.

Prevalence, Trajectories, and Predictors of Depressive Symptoms

Across all measurement occasions, approximately one-third of mothers were at risk of clinical depression. These proportions are congruent with previous research that suggested 12-49% of mothers were at risk of clinical depression.[9] These findings showed that mothers of children with new-onset epilepsy are not a homogenous group, but instead consist of distinct subgroups with different trajectories and predictors of depressive symptoms.

Four trajectories of depressive symptoms were identified by statistical modeling. The first trajectory identified was one of consistently low levels of depressive symptoms (*low stable*). Almost two-thirds of the sample fell into this trajectory. The second trajectory included one-quarter of the sample and was described as having *borderline* symptoms. These mothers had marked variations in depressive symptoms during the 24-month follow-up that straddled the CES-D cut-off score for clinical depression. The third trajectory described a group of mothers who had a *moderate increasing* symptom trajectory that was relatively stable during the first 12 months of follow-up, and then increased from 12 to 24 months. About 9% of mothers were classified as *moderate increasing*. The fourth and smallest trajectory

identified included mothers with a *high decreasing* trajectory. This trajectory had the highest CES-D score at baseline that decreased over time.

The *low stable* group had favourable characteristics that may have provided an optimal environment for mothers to cope with their child's epilepsy. With a strong and supportive family environment, as well as children with relatively good health-related quality of life, these mothers maintained low levels of depressive symptoms that remained stable during the 24-month follow-up.

Compared to the *low stable* group, the *borderline* group was younger, had worse family functioning, and fewer family resources. The variations observed in this group may reflect the challenges of managing childhood epilepsy and the unpredictable nature of seizures[1, 2] in mothers with less life experiences and compromised family circumstances.

The *moderate increasing* group was also younger, had children with cognitive problems, worse family functioning, and more family demands. This group is characterized with a moderately high CES-D score during the first 12 months that increases dramatically from 12 to 24 months after the child's diagnosis. This significant increase may be attributable to additional challenges associated with the child's health. Child cognitive problems may be an adverse event as the result of treatment with anti-epileptic drugs.[10] As well, this group has the largest proportion of children with partial seizures which are indicative of a poorer prognosis.[11] Furthermore, coping mechanisms may be challenged as mothers come to the realization that their children's illness is not going away. Such hardships or chronic strains are illustrated in the stress process model to have an impact on mothers' levels of depressive symptoms.

The *high decreasing* group had less education and lower child health-related quality of life. This group of mothers was observed to have an initially high CES-D scores that declined steadily over time. This initial experience of elevated depressive

symptoms is congruent with the stress process model that suggests the diagnosis of epilepsy in a child may have an immediate impact on the mother's mental health. It is possible that the initial distress experienced by mothers at diagnosis subsided during the 24-month follow-up as these mothers came to understand that their children's epilepsy can be managed effectively. These mothers also had family characteristics similar to mothers in the *low stable* group, which may suggest that their family environment was conducive to their improvement in depressive symptoms. Despite their reduction in depressive symptoms, mothers in the *high decreasing* group still had significantly higher depressive symptoms at 24 months compared to the *low stable* group. It remains unknown whether these mothers would have continued this trajectory where their depressive symptoms decreased to levels similar to the *low stable* group if follow-up continued past 24 months.

Impact of Depressive Symptoms on Child Health-related Quality of Life

Maternal depressive symptoms were observed to have a negative impact on both child health-related quality of life at 24 months and on the rate of change in health-related quality of life during follow-up. There was significant covariance observed in the growth curve models, indicating that children with better health-related quality of life at baseline also had greater rates of change in their health-related quality of life scores over time.

Family resources moderated the impact of maternal depressive symptoms on child health-related quality of life and the magnitude of the moderating effect varied over time. A moderator is a variable (e.g., family resources) that changes the direction or strength of the effect of the exposure (e.g., maternal depressive symptoms) on the outcome (e.g., child health-related quality of life) and can be tested by examining the effects of the exposure on the outcome across varying levels of the moderator.[12] In other words, the effect of maternal depressive symptoms on child health-related quality of life is different for mother-child dyads in families with more compared to fewer resources. In families with more resources, the negative impact of maternal

depressive symptoms on child health-related quality of life is negated, and children's health-related quality of life improves over time; however, in families with fewer resources, children's health-related quality of life worsens over time. In contrast, perception of patient-centered care was not observed to significantly moderate the relationship between maternal depressive symptoms and child health-related quality of life.

Family functioning was observed to partially mediate the impact of maternal depressive symptoms on child health-related quality of life. Similarly, family demands were also observed to partially mediate this relationship. A mediator is a variable (e.g., family functioning, demands) that lies in the causal pathway between the exposure (e.g., maternal depressive symptoms) and the outcome (e.g., child health-related quality of life).[12] In a subsequent analysis examining the mediating effect of family functioning and family demands simultaneously, the proportion of total effect mediated increased. There was no significant difference between the family functioning- and family demands-specific effects.

The results from the moderation and mediation analysis are important. Managing epilepsy at the child level through pharmacological interventions is vital; however, these results provide evidence for intervention at the family level to improve the health-related quality of life in children with newly-diagnosed epilepsy. By incorporating the entire family as the focus of care and targeting characteristics such as maternal depression, family functioning, resources, and demands, a child's health-related quality of life can be potentially improved further. Though a mother's *perception* of patient-centered care did not moderate the effect of maternal depressive symptoms on child health-related quality of life, it is unknown whether actually adopting family-centered care in the clinical setting will have a positive effect on the health-related quality of life in children with new-onset epilepsy.

The heterogeneity of depressive symptoms in mothers and its negative impact on health-related quality of life in children with new-onset epilepsy is an important

issue that requires clinical consideration by healthcare professionals caring for these children. Paediatric neurologists should be aware that epilepsy can affect the entire family and the mental health of mothers can have profound effects on the course of a child's illness. Utilizing information gained from the predictor models developed would require little time in the clinical setting and may provide important information for determining which depressive symptom trajectory a mother is likely to belong. Subsequent discussion and potential treatment of maternal depressive symptoms could then be initiated to potentially prevent or limit the impact on the child's health outcomes.

Potential Implications and Applications of Study Results

Screening for Maternal Depression

Recent research has indicated that healthcare specialists in childhood conditions, including epilepsy, are central to the successful implementation of interventions for mothers with depressive symptoms as a means to improve child outcomes based on the family-centered care approach.[13-16] Healthcare professionals caring for children with epilepsy have close contact with families that can foster trust and allow for open discussions surrounding maternal depression and its treatment. In a sample of 559 mothers with children ≤18 months of age, Kahn et al. observed that at least 85% of mothers were supportive of having their child's healthcare professional screen for depression.[17] Olson et al. found that 57% of paediatricians felt a responsibility to recognize maternal depression and 7% of these felt it was their responsibility to treat these mothers.[15] Confirming the results by Olson et al., a study by Heneghan et al. demonstrated that 77% of paediatricians surveyed identified maternal depression in their practice.[13] Of these, 82% referred mothers to another healthcare professional for treatment and 7% treated the patients themselves. The researchers reported that paediatricians who utilized at least one method to screen for maternal depressive symptoms were more than two-times more likely to either identify or

refer or treat mothers compared to paediatricians who did not screen for depression at all.

In the study by Olson et al., the majority of paediatricians used an unstructured approach to identifying depression in mothers.[15] This informal technique of identification may limit diagnosis to only more severe cases of maternal depressive symptoms, thus under-estimating the true burden of this condition and its effect on children.[18] To overcome this barrier, healthcare professionals involved in caring for children with epilepsy should consider using widely available structured questionnaires, such as the CES-D in their practices. However, due to the time required to administer some of these screening questionnaires, researchers have investigated the psychometric properties of the two-item Patient Health Questionnaire, and have shown it to yield similar detection rates of maternal depression as compared to other previously validated measures.[19, 20] This instrument has been endorsed by the United States Preventive Services Task Force and can be used by healthcare professionals in the paediatric epilepsy setting to either treat or refer mothers exhibiting depressive symptoms.[21, 22]

It is anticipated that maternal depressive symptoms can become easily over-shadowed by a presenting child's epilepsy during the medical encounter. Healthcare professionals in this situation should be active in considering how the family environment influences the illness process and *vice versa*. Healthcare professionals can find useful resources at Bight Futures (http://www.brightfutures.org).[23] This national health promotion initiative encourages paediatric healthcare professionals to support families as part of providing care to children and recommends open questioning surrounding symptoms of maternal depression.[24, 25]

In addition, healthcare professionals caring for children with epilepsy should openly discuss how maternal mood can affect child outcomes by impacting the quality of mother-child interactions and parenting behaviour. Information regarding local epilepsy centers should be provided as early in the treatment process as possible to

facilitate development of supportive social networks for families. Healthcare professionals caring for children with epilepsy cannot be expected to make formal diagnoses of depression in mothers. However, discussing the possibility of a depressive disorder and its impact on the child and providing referrals, when indicated, would be appropriate actions for paediatric healthcare professionals. Such actions may exert their effects upstream in the stress process to buffer the impact the epilepsy diagnosis has on the mental health status of mothers (Figure 1.1). Routine screening for maternal depression and communication regarding supportive resources for families may also help mothers adapt more positively to the hardships and chronic strains associated with childhood epilepsy and potentially ward off development of clinically relevant levels of depressive symptoms.

Interventions to Improve Maternal and Child Outcomes

Maternal Depression

This study demonstrated that maternal depressive symptoms negatively impact the health-related quality of life in children with new-onset epilepsy. Other population-based research has shown that mothers with depression are at particular risk of providing their children with suboptimal caregiving environments and these children are at high risk for development of early-onset psychopathology.[26] Given these important findings, it is of interest to consider whether interventions aimed at reducing depressive symptoms in mothers would result in more favourable outcomes for their children.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) is a large-scale study designed to address this issue.[27] This study provided a unique opportunity to investigate whether successful pharmacological treatment for mothers with depression would lead to improvement in psychiatric disorders and symptoms among their children. The study of outcomes in these children is referred

to the STAR*D-Child.[28, 29] In a recent study of 151 mother-child dyads followed during the year after initiation of treatment, results showed that decreases in the severity of maternal depression were significantly associated with decreases in the number of psychiatric symptoms in children.[30] Subgroup analysis showed that children whose mothers achieved remission of depressive symptoms had significantly fewer psychiatric symptoms compared to children whose mothers did not achieve remission. Furthermore, results were more favourable for children of early remitters (i.e., ≤3 months following initiation of treatment) compared to late remitters (i.e., ≥3 months following initiation of treatment). In another study using STAR*D-Child participants, remission of maternal depression was associated with improvements in child-reported parenting/family functioning, which mediated the relationship between maternal depression remission and child internalizing behaviour problems.[31]

Other researchers have investigated how non-pharmacological treatment of maternal depression can impact child behaviour problems. Verduyn et al. conducted a randomized, placebo-controlled trial to evaluate the effect of group cognitive-behavioural therapy on child behaviour problems and maternal depression in a group of 119 women with children up to four years of age.[32] Three treatment groups were evaluated: cognitive-behavioural therapy, mothers' support group, and no intervention. Significant improvements in child behaviour problems and maternal depression were observed at 12 months for those mothers randomized to cognitive-behavioural therapy, whereas no improvements were observed for mothers or children in the control groups.

Only one study has investigated reducing depression in mothers of children with epilepsy. Using a pre-/post-test quasi-experimental design, Mu and Chang developed a program to enhance resiliency by reducing family boundary ambiguity and maternal depression in a small sample of mothers of children with epilepsy.[33] The first stage of the intervention involved an assessment of parental needs, boundary ambiguity, and maternal depression completed by the child's mother. The

second and third stages involved an in-depth interview to construct the meaning of the families' experience and needs and an investigator-led educational dialogue. Three months after the intervention, there was a significant improvement in maternal depression.

These studies are encouraging. They provide evidence that successful treatment of mothers with depression may result in significant changes in the family environment, which have implications for reducing children's risk of psychopathology. Such results are congruent with the direction of causality suggested in the stress process model. This suggests the value of treating maternal depression to improve health outcomes in children. However, it is unknown whether such interventions can positively impact the health-related quality of life in children with epilepsy, or other chronic illnesses.

Family-centered Care

Evidence suggests that childhood chronic illnesses impact entire families, but also that the family environment is able to impact the illness process. DeMaso et al. demonstrated that mothers' behaviour and perceptions of child expectations, stress, and severity of the condition were better predictors of child outcomes compared to more objective clinical measures in children with congenital heart disease.[34] In their study, 33% of the variability in child adjustment was accounted for by maternal perceptions, whereas illness severity accounted for only 3% of the total variability. This suggests that healthcare professionals caring for children should adopt family-centered care strategies and be mindful of the mental and emotional state of parents since these may present avenues for intervention that can potentially improve child outcomes. Given this important preliminary work, it is important to consider whether interventions that incorporate family-centered care strategies are effective at improving child health outcomes.

A recent study by Shaw et al. addressed this issue with a sample of 731 families receiving services from a national food supplement and nutrition program.[35] Families with toddlers 2-3 years old were screened and then randomized to a brief family intervention, the Family Check-Up, which included linked interventions that were tailored and adapted to the families' needs. The Family Check-Up was originally developed as a preventive intervention to address the needs of adolescents at risk for behaviour problems and emphasizes methods to promote a family's motivation to change.[36] Results in the families with toddlers study revealed intervention effects for externalizing and internalizing problems in children and reductions in maternal depression. In addition, reductions in maternal depression mediated improvements in both children's externalizing and internalizing behaviour problems after accounting for the potential mediating effects of improvements in positive parenting.

Another example of a family-centered intervention is the Keeping Families Strong Program, which is a family-based program to promote child and family resilience in the face of maternal depression.[37] This 10-week program is delivered in a multi-family group format, with the parents meeting together and the children (aged ≥10 years) meeting weekly in a group. By involving all members of the family and utilizing a multi-family format, Keeping Families Strong aims to ensure that all family members are understood and supported, while decreasing the stigma associated with depression. Preliminary results examining Keeping Families Strong in a sample of 13 parents and 15 children suggest that the program is effective.[37] Using Cohen's recommendations for interpreting effect sizes,[38] both parents and children reported significant small to moderate reductions in children's behaviour problems, large improvements in family functioning, and moderate to large decreases in maternal depressive symptoms.

The results from these recent studies implementing family-centered care strategies are promising. The success of these programs is likely the result of adhering to the guidelines of Beardslee and Knitzer stating that family-centered interventions must

be compatible with the treatment and recovery of the parent with depression, as well as targeting aspects of family functioning, including family resilience, parent-child relationships, and cohesion,[39] which is highlighted as an avenue for intervention in the stress process model in order to improve health outcomes in children with epilepsy. However, due to the unpredictable nature of seizures, the 2.5 hour yearly in-home assessments used as part of the Family Check-Up may make this intervention less effective for families with a child with epilepsy. The biological, emotional, and social changes that occur in children and adolescents, independent of their epilepsy, may warrant more frequent meetings in a setting that allows parents and children to share their experiences with epilepsy. In addition, the use of an in-home observation by a trained "parent consultant" is likely to result in social desirability bias, whereby mothers understate their depressive symptoms and children's behaviour problems in order to appease study investigators. This bias may thus over-estimate the effect of the Family Check-Up intervention. Instead, the Keeping Families Strong program may be more amenable to use in the paediatric epilepsy population. The use of parent and child groups allows for participants to learn from each other's experiences; however, group leaders must be explicit in explaining that participants should *learn* from and not *compare* one another. Without this understanding, this program can easily have the unintended consequence of improving the health of parents and children who feel that their situation is better than another without implementing any change. On the other hand, others may become discouraged because they perceive their situation as worse than another and thus lead to deteriorating health.

Implementation of such family-centered care strategies in paediatric chronic illness populations that aim to improve outcomes other than behaviour problems, such as health-related quality of life, are clearly lacking and warrant investigation. However, implementation of hybrid programs with the goal of improving both maternal depressive symptoms and child health-related quality of life are complicated by the presence of a chronic illness in the child. Program developers must be aware of the challenges of working with families coping with a child recently diagnosed with

epilepsy. Specifically, families will likely be quite heterogeneous in terms of level of maternal depressive symptoms, epilepsy severity, presence of comorbidities in the child, and the general family environment. Thus, adaptation of programs shown to be successful in the general population should be carefully scrutinized before implemented in families with a child with epilepsy.

In addition, it is important for healthcare professionals to consider that fathers may also experience depressive symptoms in caring for a child with epilepsy. A study by Mu, showed that fathers also exhibit symptoms of depression, albeit to a lesser extent compared to mothers.[40] Although this thesis focused on maternal depressive symptoms, it is the primary caregiver's mental health that should be of interest to healthcare professionals due to the potential negative impact on child health outcomes. Thus, screening for and intervening on depressive symptoms is warranted regardless of whether the child's mother or father is the primary caregiver of a child with epilepsy.

Strengths and Limitations

Study Strengths

This study had several strengths that allowed it to overcome some of the methodological shortcomings of previous research. First, due to its national perspective and longitudinal design, this study was able to develop and empirically test complex causal pathways that answer questions about trajectories of change over time, including the identification of potential moderating and mediating processes. Previous studies in this population have been relatively small-scale, regional, cross-sectional endeavours and thus causal inferences were limited by the temporality of exposure and outcome assessment. This was the first study to prospectively investigate a cohort of mothers from the onset of their child's epilepsy.

Second, this study involved a large sample of mothers and children (n=339) followed over four time-points. There was a good response rate and retention with relatively few missing data in this study. Using a modified version of the Tailored Design Method[41] to develop a structured follow-up strategy to enhance retention rates in this motivated sample promoted completeness of the data and thus helped produce robust estimates of effect.

Third, this study investigated incident cases of epilepsy in children, rather than prevalent cases. By restricting to newly-diagnosed children, trends and trajectories early in the illness process were elucidated and provided an ideal window of opportunity for interventions aimed at decreasing maternal depressive symptoms and in turn, improving child health-related quality of life.

Fourth, the models presented in this study were novel in this research field and the complex strategies employed followed the guidelines of experts for statistical modeling of longitudinal data. Thus, robust estimates of effects could be obtained and presented in a logical and meaningful way. In addition, being mindful of the stress process, as illustrated in the theoretical framework, permitted statistically significant results observed in the causal pathway having practical implications for clinicians, researchers, and families involved in the care of children with epilepsy.

Study Limitations

Despite the novel contributions of this research to the academic field, there are a few limitations that must be considered. Since this study was a secondary data analysis of HERQULES, the limitations are discussed in the context of the larger study. First, measurement occasions were not based on empirical evidence of depressive symptoms trajectories; instead data collection was guided by the clinical course of epilepsy and associated follow-up appointments with paediatric neurologists. However, it was believed that the measurement occasions were close enough together to avoid missing potential fluctuations in maternal depressive

symptoms and distanced enough to allow for sufficient time to detect important changes. Three assessments were completed in the first 12 months, since during this time maternal and family factors and clinical management of epilepsy were hypothesized to be relatively dynamic. Whereas, in the second year, circumstances were believed to stabilize and thus an assessment at 24 months was deemed appropriate. In addition, since it was impossible to recruit patients and their families prior to diagnosis, this study was unable to capture true baseline data, especially for maternal depressive symptoms. However, "baseline" data were collected within a short period after diagnosis. Nonetheless, results from this study may have been affected by incidence-prevalence bias.[42]

Second, the inclusion criteria for HERQULES included an age criterion of 4-12 years and thus results may not be valid if extrapolated to families with children with epilepsy outside of this age range. Children younger than four years were excluded because many suffer from catastrophic forms of epilepsy that are difficult to diagnose and have a known negative impact on the family. As well, several of the measurement instruments have not been validated for children less than four years of age. Since the focus of HERQULES was on child and family factors, the upper age range was limited to children 12 years of age. This is because at the beginning of adolescence (i.e., 13-14 years), the sphere of influence on children broadens considerably to include peers.

Third, only parents' perceptions of child and family factors were considered in HERQULES and these may differ from that of the neurologist or child with epilepsy. The results from this study suggest that mothers of children with new-onset epilepsy, regardless of their mental health status, are valid informants of various aspects of their child's health outcomes. Only one discrepancy was observed between mothers' and neurologists' reports. Mothers with low levels of depressive symptoms reported similar outcomes as neurologists when evaluating disruptions in daily activities due to the child's epilepsy. That is, as neurologists reported better functioning, so did mothers. But, mothers with high levels of depressive symptoms

systematically reported higher scores in children regardless of the neurologists' reports. Although it is important to consider both child and parent perceptions on the illness process, this would have introduced several methodological complexities into HERQULES. A mail survey design was the only viable strategy for data collection given the national scope of the study and it could not be ascertained as to whether children completed the questionnaires independently. As well, it has been determined that on average, only children eight years of age or older can reliably self-report.[43-46] This would have resulted in a data for only a fraction of participants.

Fourth, this study hypothesized a direct effect of maternal depressive symptoms on child health-related quality of life, as well as effects moderated and mediated by family environment variables. This hypothesis was guided by the theoretical underpinnings of Pearlin's stress process model[47-49] and empirical evidence from previous research examining the antecedent-consequence relationship between maternal depressive symptoms and child outcomes[50-52] and the casual link between maternal depressive symptoms, family environment, and child health outcomes.[53-57] For example, Elgar et al. used the National Longitudinal Survey of Children and Youth to show that maternal depressive symptoms tended to precede child aggression and hyperactivity in children aged 4-11 years.[51] In a subsequent study by Elgar et al., parenting quality (as a measure of family functioning) mediated the impact of maternal depressive symptoms on child and adolescent maladjustment over a two-year period among 10-15 year old youth sampled in the National Longitudinal Survey of Children and Youth.[56]

Despite such evidence supporting this direction of causal effect, one may speculate whether the direction of effects may be reversed, such that changes in child health outcomes lead to changes in maternal depressive symptoms. In a study of mothers of children with difficult temperament 3-6 years of age, Gartstein and Sheeber observed that child behaviour problems predicted maternal depressive symptoms and this relationship was mediated by measures of family functioning during a 12-month follow-up.[58] In another study, Weaver et al. reported that maternal

depressive symptoms mediated the relationship between parenting self-efficacy (a measure of family functioning) and child behaviour problems in a sample of mothers of children aged 2-4 years.[59]

In such circumstances, applying Hill's criteria for causation[60] does not help to elucidate which mechanism is correct since each is possible, not to mention the concept of reciprocal effects. Given the feasibility and potential ethical restraints in determining the direction of causality, the best that researchers can do is present a case for their chosen causal mechanism that decreases the probability that an alternative mechanism is operating. This study was a secondary data analysis of HERQULES in which the objective was to examine the health-related quality of life of children with epilepsy. Extending this outcome within the context of the family environment, it was reasonable for this study to posit maternal depressive symptoms as the exposure, child health-related quality of life as the outcome, and family environment factors as moderators and mediators of this relationship.

Conclusions and Future Directions

This study demonstrated that approximately one-third of mothers of children with newly-diagnosed epilepsy are at risk for clinical depression during the first 24 months after diagnosis. This group of mothers is not homogeneous, instead four distinct trajectories of depressive symptoms were observed during the follow-up and each trajectory had its own unique set of predictors for group membership. Importantly, a negative relationship was observed between maternal depressive symptoms and child health-related quality of life. This relationship was moderated by family resources and mediated by family functioning and family demands.

Future work should continue with this population and sample of mothers and children to understand the long-term effects of depression on child health-related quality of life. This would follow similar studies conducted by Sillanpaa et al. in Finland of incidence, prognosis, and quality of life in adults who had epilepsy in

childhood.[61-64] Questions relating to whether maternal depressive symptoms early in a child's illness predict later health outcomes and how the impact of the family environment changes as the child grows through adolescence into young adulthood can be investigated. Such research may further highlight the importance of early intervention to prevent or dampen the negative effect of maternal depressive symptoms on health-related quality of life in individuals with epilepsy.

In addition, this work would benefit from testing the models developed throughout the course of this research in external samples of mothers of children with epilepsy. Such work could provide important validation for the models, thus increasing their clinical utility for healthcare professionals caring for children and families with epilepsy. Examining models in both incident and prevalent cases of epilepsy would broaden the utility of these models.

Development of a family-centered intervention for families with a child with epilepsy is another important undertaking that is a logical follow-up to this study. This intervention should follow the examples set by similar programs in other populations, but adapted for childhood epilepsy. This could be feasibly accomplished with the inclusion and support of the Epilepsy Support Centre in London. A systematic approach to implementing such a program would be to conduct pilot studies at the local or regional level in order to determine the feasibility of such an intervention. From there, randomized controlled trials comparing the intervention to a suitable control will permit a better understanding of the effectiveness of the intervention and whether there is merit in adopting such a program into standard clinical care for families who are impacted by both depression and epilepsy. A systematic program evaluation for this intervention should also become an active area of family-centered care research. By addressing the needs and building on the strengths of the family the harmful effects of maternal depressive symptoms on outcomes in children with epilepsy can be prevented and reduced.

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Appendix A
Appendices
Data Collection

The data for this study come from the Health-related Quality of Life of Children with Epilepsy Study (HERQULES), a national prospective cohort study in which children aged 4-12 years with new-onset epilepsy in Canada were followed for 24 months.[1]

Study Design

Measurement occasions for assessment were post-diagnosis (baseline), and 6, 12, and 24 months later. Since there is no precedent for determining the optimal measurement occasions at which to collect data to accurately capture the course of health-related quality of life in childhood epilepsy, the specified measurement occasions were selected based on the following *a priori* considerations for the original protocol: 1) data should be captured as close to the date of diagnosis as possible to capture the immediate impact of diagnosis on health-related quality of life and any factors hypothesized to affect health-related quality of life; 2) measurement occasions should be close enough together to avoid missing potential fluctuations in both predictor and outcome variables; and, 3) measurement occasions should be distanced enough to allow for sufficient time to detect important changes in variables and to avoid participant fatigue. Three assessments were completed in the first 12 months since during this time family factors and clinical management are hypothesized to be relatively dynamic. Whereas, in the second year, circumstances are believed to stabilize and thus an assessment at 24 months was deemed appropriate.

Sample Characteristics

The study population was mothers whose children were receiving care from a paediatric neurologist in Canada for new-onset epilepsy. Patients were recruited

prospectively over a 36-month period from April 2004 to April 2007. Parents of each consecutive child diagnosed with epilepsy were approached to participate in the study. The inclusion criteria for patients were as follows: 1) new case of epilepsy (≥2 unprovoked seizures), in whom diagnosis of epilepsy has not been previously confirmed, seen for the first time by a participating paediatric neurologist within the data collection period; 2) epilepsy diagnosed between the ages of 4-12 years; and, 3) parent must have been primarily responsible for the child's care for ≥6 months and continue to be for the duration of the study. Children with newly-diagnosed epilepsy with a prior history of neonatal seizures were included if medication was removed by six weeks of age without recurrence. Patients were excluded from the study if: 1) diagnosis of epilepsy had been previously confirmed by another physician; 2) diagnosed with other progressive or degenerative neurological disorder (e.g., mental retardation); 3) diagnosed with other major co-morbid non-neurological disorders that would have an impact on quality of life (e.g. asthma requiring daily medication, renal failure); and, 4) parent had insufficient English language skills to complete questionnaires. In addition to these criteria for HERQULES, this research excluded parent questionnaires completed by anyone other than the patient's mother (i.e., biologic, adoptive, foster). International League Against Epilepsy (ILAE) guidelines for the implementation of observational studies in childhood epilepsy were adopted in an effort to generate robust findings comparable with past and future investigations.[2] Types of seizure and epilepsy syndrome were classified in terms of ILAE's 1981 and 1989 classification system, respectively.[3, 4]

Data Collection Strategy

Investigators from HERQULES used a modified version of the Tailored Design Method (TDM) in designing a mail survey study to assess health-related quality of life in children diagnosed with epilepsy.[5] The TDM applies a set of guidelines and procedures shown to be effective in producing high quality data and attaining high participation and retention rates.[5] Participant recruitment for HERQULES occurred in two stages. All practicing paediatric neurologists in Canada who reported caring

for children with new-onset epilepsy were invited to participate in the study. Neurologists were asked to identify all children receiving a new diagnosis of epilepsy who met the inclusion criteria and to subsequently introduce HERQULES to families.

Physician Recruitment

All paediatric neurologists practicing in Canada were approached to participate in HERQULES. The current membership list of the Canadian Association of Child Neurology (CACN) served as the sampling frame.[6] Although the CACN is a voluntary association, almost all paediatric neurologists currently practicing in Canada are members. This resulted in a sample of 103 paediatric neurologists. To ensure inclusiveness, a small panel of members from across the country reviewed the list and added the names of a small number of paediatric neurologists who were not on the list and excluded a few members who were no longer practicing. Neurologists were excluded from the list if they did not treat paediatric epilepsy. Through this process, the sampling frame was reduced to a total of 72 eligible members, all of whom agreed to participate. A total of 53 paediatric neurologists (74%) recruited participants. The remainder either did not see a patient meeting the inclusion criteria during the recruitment period or enrolling participants was not feasible given the constraints of their clinical practice. At the initiation of the study, physicians were provided with all study material in a prepared package including an overview of the study, physician-report forms, study timelines, inclusion/exclusion criteria documentation, and a token of appreciation. The study package oriented the physician to the study and attempted to increase its feasibility within the constraints of their clinical practice, by providing all necessary study documents. Throughout the study, physicians were sent 2-3 newsletters annually describing study updates and reminders. Neurologist participation included two components: 1) approaching the family to introduce HERQULES; and, 2) providing clinical information regarding the child's epilepsy at four measurement occasions for each consenting patient. In order to minimize loss of data, participating neurologists

were also sent an individualized physician report approximately every six weeks listing the physician's patient data not yet returned to the investigators.

Parent Recruitment

Paediatric neurologists and their healthcare teams identified consecutive patients who met the inclusion criteria during the recruitment period. When a paediatric neurologist identified an eligible patient, he/she approached the parents with information regarding HERQULES. If parents agreed to be contacted by investigators, they signed a release of information that was faxed to the HERQULES office so that a letter of information outlining HERQULES and the requirements of participation could be mailed. Within a few days of receiving the letter, investigators contacted the family to address questions and to determine participation status. Primary caregivers were asked to complete a questionnaire that required approximately 45-60 minutes. The post-diagnosis questionnaire was sent to families to complete upon consent to participate. Subsequent questionnaires were mailed 6, 12, and 24 months after diagnosis. The questionnaire was rated at a grade seven level using the Flesch-Kincaid Grade Score.[1, 7] The questionnaire included measurement tools assessing child health-related quality of life, family demands, functioning, and resources, parental depressive symptoms, parents' perception of patient-centered care, and demographic factors. A small financial token of appreciation was included with every questionnaire mailed. At the final contact at 24 months, parents were given the opportunity to specify if they would like to receive a summary of the study results, which were prepared upon study completion. There were 456 eligible participants identified in HERQULES between April 2004 and April 2007, 97% of whom consented to take part in the study. Figure A.1 is a diagram of the complete study hierarchy.

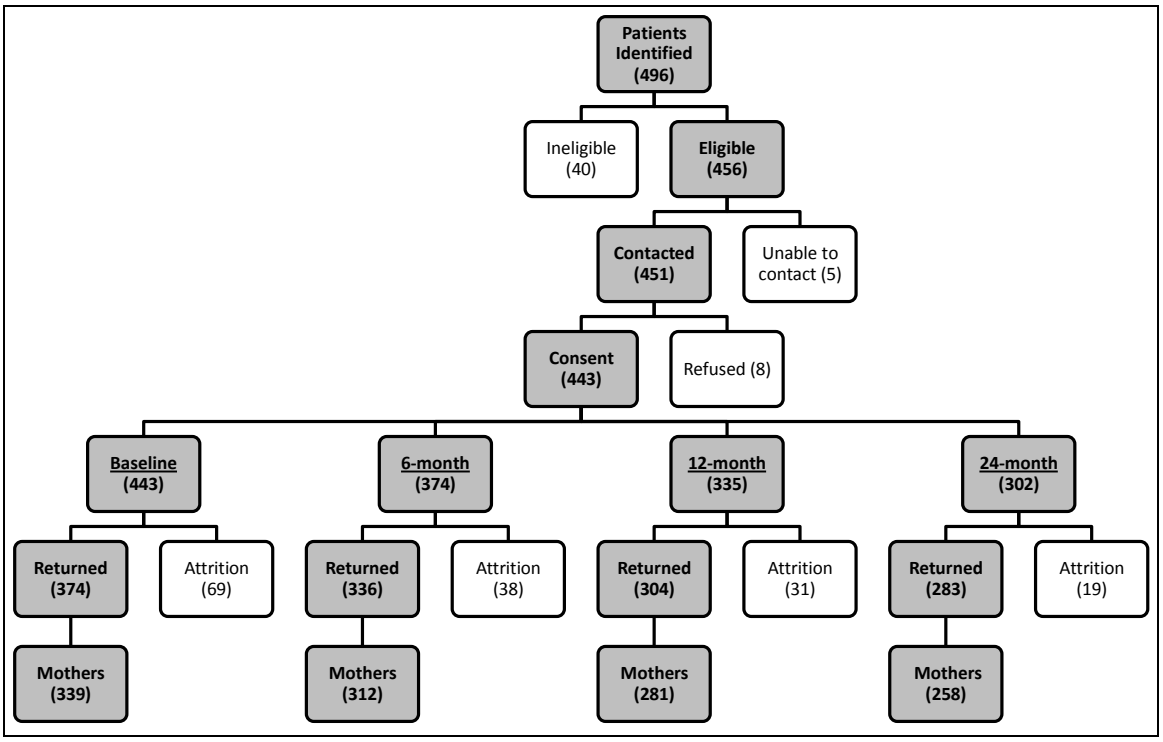

Figure A.1. Study Hierarchy for HERQULES.

Data Management

Epilepsy characteristics completed by paediatric neurologists were recorded at each study site and faxed or mailed to the HERQULES office in the Department of Paediatrics at the Children's Hospital of Western Ontario in London, Canada. Parent questionnaires were mailed directly to the HERQULES office for data entry, analysis, and quality control. Completed questionnaires received by the HERQULES office were examined to remove any identifying information and to ensure that all sections were completed. If sections were missing, parents were contacted and sent the missing sections for completion. Data were entered by graduate students in the Department of Epidemiology and Biostatistics, at The University of Western Ontario throughout the data collection period with Statistical Package for the Social Sciences (SPSS, Windows build 16, SPSS Inc., Chicago, IL). Any responses not accommodated by the established coding structure were brought to the attention of other study personnel and the principal investigator. All decisions made during the process of entering data were recorded in a log for quick reference for other data entry

personnel. Data verification was performed on 100% of entered data by research assistants other than those who initially entered the data. Data correction logs were maintained and corrections were made by the student who originally entered the data.

Ethical Approval

Approval for the original HERQULES protocol was obtained from all relevant research ethics board across the country. A revised approval to conduct the proposed study was sought from the Research Ethics Board at The University of Western Ontario and obtained prior to starting work on this study (Appendix B).

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Appendix B

Ethics Approval

Due to margin requirements, statements of ethical approval to conduct this research are shown on subsequent pages.

Office of Research Ethics

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. K.N. Speechley
Review Number: 10069E
Revision Number:
Protocol Title: Health-Related Quality of Life in Children with Epilepsy: The First Two Years After Diagnosis Through Parents' Eyes
Department and Institution: Paediatrics, Children's Hospital of Western Ontario
Sponsor: CIHR
Approval Date: 18-Nov-03
End Date: 31-Mar-08
Documents Reviewed and Approved: UWO Protocol, Letters of Information & Consent

Documents Received for Information:

This is to notify you that the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has received and granted expedited approval to the above named research study on the date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

This approval shall remain valid until end date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;

b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interset, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB (Expedited): Dr. Paul Harding

Karen Kuenerman, BA (Hons), Ethics Officer HSREB (Expedited)
E-mail: kuenaman@uwo.ca

Faxed: ON
Date: Nov. 19/03

This is an official document. Please retain the original in your files.

Western

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. K.N. Speechley

Review Number: 10069E **Revision Number:** 5

Review Date: August 20, 2008 **Review Level:** Expedited

Protocol Title: Health-Related Quality of Life in Children with Epilepsy: The First Two Years After Diagnosis Through Parents' Eyes

Department and Institution: Paediatrics, Children's Hospital of Western Ontario

Sponsor: CIHR

Ethics Approval Date: August 20, 2008 **Expiry Date:** September 30, 2009

Documents Reviewed and Approved: Revised study team.

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Paul G. Harding

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland (jsutherl@uwo.ca)	☐ Elizabeth Wambolt (ewambolt@uwo.ca)	☑ Grace Kelly (grace.kelly@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

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cc: ORE File
LHRI

Appendix C

Measurement

Measures used in the study are briefly summarized in Table C.1 and the complete study package is shown in Appendix D. Study variables included maternal, child and family factors.

Maternal Depressive Symptoms

Maternal depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item questionnaire that measures depressive symptoms in the general adult population.[1] The CES-D is a self-report scale which is an amalgamation of previously devised depressive inventories, including the Beck Depression Inventory, Zung's depression scale, a scale developed by Raskin, and a scale developed by the Minnesota Multiphasic Personality Inventory. The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. The response values are four-point Likert scales, with range 0-3, and anchor points in terms of days per week "rarely or none of the time (less than one day)" to "most or all of the time (5-7 days)". The final score spans from 0-60, with a higher score indicating greater impairment. Four of the items (items 4, 8, 12, 16) are positively worded and therefore are reverse-scored. Individuals with a final score of ≥16 are typically identified as a depressive case. This generally represents an individual who has reported ≥6 items to be frequently present over the course of the previous week, or most of the 20 items to be present for a shorter duration.

Among community samples, internal consistency estimates range from 0.80-0.90; test-retest reliability, ranging from two weeks to one year, is reported to be between 0.40-0.70.[1, 2] Four factors have consistently, but not always, been reported for the CES-D: depressed affect, positive affect, somatic and retarded activity, and

interpersonal.[1-4] The factors appear to be robust across time and populations varying in ethnicity and health.[2, 4, 5] An important early validation of the CES-D was done by Weissman et al.[6] The scale demonstrated acceptable concurrent and discriminant validity in a study of a large two-site community sample and a sample of psychiatric patients. It was able to discriminate between psychiatric patients being treated for depression and other psychiatric patients, as well as to identify patients with a secondary diagnosis of depression among those with a primary diagnosis of alcoholism, drug addiction, and schizophrenia. High sensitivity and specificity were reported for people with major depression, schizophrenia, and alcohol dependence. Recent studies using the CES-D have aimed to understand depressive symptoms among chronically ill persons,[7-9] and their caregivers.[10, 11]

Family Environment

Three aspects of family environment (demands, functioning, resources) were measured based on parent-report. Family demands were quantified using the Family Inventory of Life Events and Changes (FILE) developed by McCubbin et al., which assesses the pile-up of simultaneous normal and non-normal life events and changes in life events experienced by a family during the previous year.[12] As a family life events inventory, all events experienced by any single member are recorded. This is because, in the context of a family systems perspective, a change in any one family member likely affects other family members to a varying degree. The 71 items in the FILE are grouped into nine scales assessing various strains: intra-family, marital, pregnancy/childbearing, finance and business, work-family transitions, illness and family care, losses, transitions in and out, and legal. The FILE is designed to be administered to adult members of the family unit. The score is computed by giving each "yes" response a score of one. Summing all "yes" responses provides a score for each subscale and the total pile-up score. The reliability and validity of the FILE is well-established.[12] As measured by Cronbach's α, the overall reliability of the FILE is 0.72. The overall scale reliability is α=0.81 with the subscale scores ranging from 0.30-0.73. This indicates that internal consistency is most

stable for the entire FILE scale, with each subscale being less stable. As well, test-retest reliability investigations showed correlations ranging from 0.72-0.77, indicating acceptable reliability over time. Initial examinations of validity demonstrated strong discriminant validity comparing low and high conflict families with cerebral palsy, with high conflict families experiencing a significantly higher pile-up of life events and changes.

The Family Adaptability, Partnership, Growth, Affection, and Resolve (Family APGAR), developed by Smilkstein, was the instrument used to assess satisfaction with family relationships.[13] It was designed on the premise that the perception of family functioning could be assessed by a family member's self-report of satisfaction with the following five parameters: adaptation (assistance received when family resources are needed); partnership (mutuality in family communication and problem solving); growth (freedom to change roles and attain physical and emotional maturation); affection (intimacy and emotional interaction among members); and, resolve (time commitments made to the family by members). The Family APGAR is a five-item instrument completed by an adult family member and responses are based on a five-point Likert scale, ranging from 0-4 for each item. The total score is computed by summing each item score, ranging from 0-20. Higher scores on the Family APGAR are indicative of higher satisfaction with family functioning. The Family APGAR has been found to be valid and reliable in both the clinical and research setting with adults and children.[13-15] Reliability analyses have demonstrated an internal consistency of Cronbach's α=0.80 and test-retest reliability of 0.83.[15]

In an attempt to assess the repertoire of resources available to aid families adaptation to stressful events, the Family Inventory of Resources for Management (FIRM), developed by McCubbin et al. was used in this study.[16] The items included in the FIRM were influenced by theory and empirical findings in the areas of personal resources, family system internal resources, and social support. The 68-item, self-report instrument is completed by an adult family member and includes four scales

representing perceived family resources. The scales include family esteem and communication, family mastery and health, extended family social support, and financial well-being. For this study, only two scales (family mastery and health, extended family social support) which have been found to be associated with adaptation to childhood epilepsy were used.[17] The family mastery and health subscale includes 20 items that reflect family resources with the following dimensions: 1) sense of mastery over events and outcomes; 2) family mutuality; and, 3) physical and emotional health. The extended family social support subscale is four items and reflects the mutual help and support given to and received from relatives. Scoring procedures for the FIRM involve summing all response values, which range from 0 (not at all) to 3 (very well) to provide a total FIRM score. The FIRM has demonstrated adequate reliability and validity properties.[16] The internal consistency for the four subscales is Cronbach's α=0.89, with individual reliabilities for the family mastery and health and extended family social support subscales of 0.85 and 0.62, respectively. Significant correlations between the FIRM and family environment dimensions of cohesion, expressiveness, conflict, and organization ($p<0.01$) of the Family Environment Scale, indicate adequate criterion (concurrent) validity of the FIRM.

Epilepsy Characteristics

Physicians completed a two-page questionnaire documenting the clinical factors of each patient's epilepsy including: severity of epilepsy, seizure type and frequency, type of epilepsy syndrome, age at onset and diagnosis, medication information, adverse effects, other major co-morbidities, gender, and age. Severity of epilepsy was classified using the Global Assessment of Severity of Epilepsy (GASE), a single-item measure developed for HERQULES. With the GASE, neurologists rate the overall severity of each child's epilepsy using a seven-point scale ranging from 1=extremely severe to 7=not at all severe. The GASE demonstrated minimum burden on participants, adequate validity, and high intra- and inter-rater reliability.[18]

Child Health-related Quality of Life

To assess child health-related quality of life, parents completed a generic and epilepsy-specific instrument. The Child Health Questionnaire Parent Form-50 (CHQ) is a 50-item, parent-rated, generic questionnaire assessing child health, well-being, and the impact of illness on life function during the previous four weeks.[19] The CHQ was designed as a multidimensional profile of health-related quality of life and was the first comprehensive paediatric health-related quality of life measure developed with norms for children <18 years of age and established reliability and validity in both healthy and chronically ill children, including epilepsy.[19-27] Each of the CHQ dimensions is measured with multiple items, with higher scores indicating better health-related quality of life. Parents respond to items along a four- to six-level response continuum to capture both the presence and the extent of limitations during the previous four weeks. The CHQ provides individual scale scores for each of the 13 concepts measured and two summary scores for physical and psychosocial health. Nine concepts focus on the child, which include physical functioning; limitations in schoolwork and activities with friends due to emotional/behavioral difficulties; limitations in schoolwork and activities with friends due to physical health; bodily pain/discomfort; general behavior; mental health; self-esteem; general health perceptions; and change in health. The remaining four concepts measure impact on the family: parental impact-time; parental impact-emotional; family activities; and family cohesion. Two weighted and standardized summary scores assessing physical and psychosocial functioning are calculated, with a mean of 50 and a standard deviation of 10. The physical health summary scale measures the child's general health, pain, and limitations in physical and social activities due to health. The psychosocial health summary scale measures the child's self-esteem, mental health, and the impact of the illness on physical and social activities. The scale also measures the impact of illness on the family.

The Quality of Life in Childhood Epilepsy (QOLCE) is a multifaceted, parent-report, epilepsy-specific instrument for evaluating health-related quality of life of children

with epilepsy aged 4-18 years. The QOLCE was developed from an original questionnaire containing 91 items.[27] Item analysis and validation in North America led to a final questionnaire containing 76 items with 16 subscales spanning seven domains of life function including, physical activities, social activities, cognition, well-being, behavior, general health, and general quality of life.[28] Items are rated on a five-point Likert scale, which are used to calculate the 16 subscale scores ranging from zero (low functioning) to 100 (high functioning). The subscale scores are averaged to produce an overall health-related quality of life score. It has demonstrated good construct validity, internal consistency reliability (0.72-0.93), and sensitivity to epilepsy severity.[27]

Perception of Patient-centered Care

Based on the Patient-Centered Model of Care, a modified version of the Patient Perception of Patient-centeredness (PPPC) was used to assess parents' perceptions of the extent to which the healthcare services (i.e., interaction with the paediatric neurologist) their child received were patient-centered.[29] Seven of the original 14 items were slightly modified to make them appropriate for parent-report by replacing "your" with "your child's" and "you" with "your child". A total score, as well as subscale scores on "exploring the disease and illness experience" (items 1-4), and "finding common ground" (items 5-13) can be formed.[29] The PPPC is coded so that low scores correspond to positive perceptions. The total score is calculated by summing the all item responses and dividing by the number of items completed. Subscale scores are determined by calculating their mean scores. While test-retest reliability has not been assessed, inter-item reliability has been found to be adequate for the PPPC (Cronbach's α=0.71).[30] The validity of the PPPC was established through a significant correlation with the Measure of Patient-centered Communication (r=0.16; p=0.01) and significant correlation with patient health outcomes and with the efficiencies in the use of health services.[30] The adapted version was pre-tested on a sample of 59 parents of patients being seen by a paediatric neurologist in London, Ontario. The participation rate was 100%. It took

parents 1-4 minutes to complete with an average of three minutes. No ceiling or floor effects were detected.

Demographic Characteristics

Questions regarding demographic characteristics of families, including parent age, education, marital status, employment status, and household income were adapted from previous studies employing these items successfully.

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Table C.1. Summary of Variables from HERQULES Considered for Inclusion.

Variable	Measure	Scale of Measurement	
		Original	**Analysis**
Maternal			
<u>Demographics</u>			
Age	Date of birth	Continuous	NC
Marital status	Current marital status	Nominal 1. Married 2. Widowed 3. Divorced 4. Separated 5. Remarried 6. Never married	Nominal 1. Married* 2. Not married
Education	Highest level of completed education	Ordinal 1. <8 years 2. 8-12 years 3. Completed high school 4. Completed technical training 5. Completed college or university 6. Completed graduate school	Ordinal 1. Less than high school 2. Completed high school 3. Completed technical training 4. Completed college or university
Employment status	Current employment status	Nominal 1. Not working due to child's health	Nominal 1. Not working 2. Homemaker

		2. Not working for other reasons 3. Looking for work outside the home 4. Working full- or part-time, inside or outside the home 5. Full-time homemaker 6. Student	3. Student 4. Working
Parity	Number of children in household	Ordinal	NC
<u>Mental Health</u>			
Depressive symptoms	CES-D	Continuous	NC
Child			
<u>Demographics</u>			
Age	Date of birth	Continuous	NC
Gender	Child sex	Nominal 0. Female 1. Male	NC
<u>Epilepsy Factors</u>			
Family history	Presence of family history of epilepsy	Nominal 1. No 2. Yes	NC

Illness Severity	GASE	Ordinal 1. Extremely severe 2. Very severe 3. Quite severe 4. Moderately severe 5. Somewhat severe 6. A little severe 7. Not at all severe	NC
Duration	Age at onset subtracted from date of baseline survey	Continuous	NC
Seizure classification	Broad classification of seizures	Nominal 1. Generalized 2. Partial	NC
Seizure type	Specific subtype of seizures	Nominal 1. Primary generalized 2. Absence 3. Simple/complex partial 4. BECRS 5. Secondary generalized 6. BECRS & secondary generalized 7. Undetermined	NC
Age at onset	Age of seizure onset	Continuous	NC
Medication use	Current and total number of anti-epileptic drugs prescribed	Continuous	NC

Behaviour	Severity of behaviour problems	Ordinal 1. None 2. Mild 3. Moderate 4. Severe	NC
Cognitive	Severity of cognitive disability	Ordinal 1. None 2. Borderline 3. Mild 4. Moderate 5. Severe	NC
Motor	Severity of motor limitations	Ordinal 1. None 2. Mild 3. Moderate 4. Severe	NC
<u>Health</u>			
Health-related quality of life	QOLCE CHQ	Continuous Continuous	NC NC
Family			
<u>Demographics</u>			
Income	Gross annual household income	Ordinal 1. <$10,000 2. $10,000-19,999	Ordinal 1. <$20,000 2. $20,000-39,999

		3. $20,000-29,999 4. $30,000-39,999 5. $40,000-49,999 6. $50,000-59,999 7. $60,000-69,999 8. $70,000-79,999 9. $80,000-89,999 10. $90,000-99,999 11. >$100,000 12. Don't know	3. $40,000-59,999 4. $60,000-79,999 5. >$80,000 6. Don't know
Family Factors			
Demands	FILE	Continuous	NC
Functioning	Family APGAR	Continuous	NC
Resources	FIRM	Continuous	NC
Perception of Healthcare			
Patient-centered care	PPPC	Continuous	NC

NC, no change.
*Includes mothers in married and common-law relationships.

Appendix D

Study Package

The complete HERQULES study package is contained in this Appendix, including both the parent and physician forms. Specific measurement instruments can be found in the following sections of the study package.

Section 1: Quality of Life in Childhood Epilepsy (QOLCE)
Section 2: Patient Perception of Patient-centered Care (PPPC)
Section 3: Family Inventory of Resources for Management (FIRM)
Section 4: Family Inventory of Life Events and Changes (FILE)
Section 5: Family Adaptability, Partnership, Growth, Affection, Resolve (APGAR)
Section 6: Center for Epidemiological Studies Depression Scale (CES-D)
Section 7: Measure of Processes of Care (MPOC-20)
Section 8: Child Health Questionnaire – Parent Form (CHQ)
Section 9: Demographics

Physician Form

Study I.D: _ _ _ _ _

Child Health
Research Institute

HERQULES STUDY

Health Related Quality of Life in Children with Epilepsy: The First Two Years After Diagnosis Through Parents' Eyes

Parents' Questionnaire

Q1

Throughout this questionnaire when we refer to "your child", we are referring to your child with the initials ____ ____. Please keep this child in mind when responding to the questions.

Revised version 4, November 8, 2006

Q1

Study ID _ _ _ _

I have received $5.00 as a token of appreciation for my participation in the HERQULES Study with Dr. Kathy Nixon Speechley in London Ontario.

Date: _____ Initial: _____

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.**

SECTION 1:

YOUR CHILD'S PHYSICAL ACTIVITIES

The following questions ask about physical activities your child might do.

1.1. In his/her daily activities during the past 4 weeks, how often has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. needed special precautions (i.e. wearing a helmet)?	☐	☐	☐	☐	☐	☐
c. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
e. gone swimming? (i.e. swam independently)	☐	☐	☐	☐	☐	☐
f. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
g. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
h. played with friends away from you or your home?	☐	☐	☐	☐	☐	☐
i. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
j. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

1.2. 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 tired	☐	☐	☐	☐	☐	☐
b. felt energetic	☐	☐	☐	☐	☐	☐

1.3. Is there anything else you would like to tell us about your child's activities?

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 calm?	☐	☐	☐	☐	☐	☐
c. felt helpless in situations?	☐	☐	☐	☐	☐	☐
d. felt happy?	☐	☐	☐	☐	☐	☐
e. wished s/he was dead?	☐	☐	☐	☐	☐	☐
f. felt in control?	☐	☐	☐	☐	☐	☐
g. felt tense and anxious?	☐	☐	☐	☐	☐	☐
h. felt frustrated?	☐	☐	☐	☐	☐	☐
i. felt overwhelmed by events?	☐	☐	☐	☐	☐	☐
j. worried a lot?	☐	☐	☐	☐	☐	☐
k. felt confident?	☐	☐	☐	☐	☐	☐
l. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
m. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
n. got easily embarrassed?	☐	☐	☐	☐	☐	☐
o. felt different or singled out?	☐	☐	☐	☐	☐	☐
p. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
q. felt valued?	☐	☐	☐	☐	☐	☐
r. felt s/he was not good at anything?	☐	☐	☐	☐	☐	☐
s. felt no one cared?	☐	☐	☐	☐	☐	☐

1.5. Is there anything else you would like to tell us about how your child feels in general?

4

COGNITION

The following questions ask about some problems children have with concentrating, remembering, and speaking.

1.6. Compared to other children of his/her own age, how often during the past 4 weeks has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. had difficulty attending to an activity?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said & done?	☐	☐	☐	☐	☐	☐
i. completed activities that needed organising/planning?	☐	☐	☐	☐	☐	☐
j. found it hard remembering things?	☐	☐	☐	☐	☐	☐
k. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
l. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐
n. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
o. planned to do something then forgot?	☐	☐	☐	☐	☐	☐
p. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
q. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐
r. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
s. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
t. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
u. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
v. had trouble writing?	☐	☐	☐	☐	☐	☐
w. had trouble talking?	☐	☐	☐	☐	☐	☐

1.7. Is there anything else you would like to tell us about your child's concentration, memory or speech?

YOUR CHILD'S SOCIAL ACTIVITIES

1.8. During the past 4 weeks, how often has your child's epilepsy:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours)?	☐	☐	☐	☐	☐	☐
b. helped him/her to make friends?	☐	☐	☐	☐	☐	☐
c. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
d. improved his/her friendships & relationships with others?	☐	☐	☐	☐	☐	☐
e. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
f. isolated him/her from others?	☐	☐	☐	☐	☐	☐
g. improved his/her relations with family members?	☐	☐	☐	☐	☐	☐
h. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐
i. frightened other people?	☐	☐	☐	☐	☐	☐

1.9. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?

☐ Yes, limited a lot ☐ Yes, limited some ☐ Yes, limited a little ☐ Yes, but rarely ☐ No, not limited

1.10. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with friends?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost Never ☐ Not applicable

1.11. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with family?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost Never ☐ Not applicable

1.12. Is there anything else you would like to tell us about your child's social activities?

YOUR CHILD'S BEHAVIOUR

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. relied on you/family to do things for him/her that s/he was able to do him/herself	☐	☐	☐	☐	☐	☐
b. asked for reassurance	☐	☐	☐	☐	☐	☐
c. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
d. wanted things to be perfect	☐	☐	☐	☐	☐	☐
e. did not give up easily	☐	☐	☐	☐	☐	☐
f. angered easily	☐	☐	☐	☐	☐	☐
g. hit or attacked people	☐	☐	☐	☐	☐	☐
h. swore in public	☐	☐	☐	☐	☐	☐
i. joined in activities with other children	☐	☐	☐	☐	☐	☐
j. feared unfamiliar places, situations or people	☐	☐	☐	☐	☐	☐
k. preferred his/her own company instead of seeking out others	☐	☐	☐	☐	☐	☐
l. was obedient	☐	☐	☐	☐	☐	☐
m. set high standards for self	☐	☐	☐	☐	☐	☐
n. did not worry about what others thought	☐	☐	☐	☐	☐	☐
o. get along with other children	☐	☐	☐	☐	☐	☐
p. wished s/he was someone or somewhere else	☐	☐	☐	☐	☐	☐
q. acted without thinking	☐	☐	☐	☐	☐	☐
r. demanded a lot of attention	☐	☐	☐	☐	☐	☐

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
s. was decisive	☐	☐	☐	☐	☐	☐
t. was independent	☐	☐	☐	☐	☐	☐
u. preferred routines or disliked changes	☐	☐	☐	☐	☐	☐
v. did things just to prove s/he could	☐	☐	☐	☐	☐	☐
w. preferred the company of adults	☐	☐	☐	☐	☐	☐

1.14. Is there anything else you would like to tell us about your child's behaviour?

GENERAL HEALTH

1.15. Compared to other children his/her age, how do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question.

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

1.16. Is there anything else you would like to tell us about how epilepsy has affected your child's health?

QUALITY OF LIFE

1.17. In the past 4 weeks what has your child's quality of life been?

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

1.18. Consider your child's present skills in thinking, learning, remembering, speaking and understanding. Taken together, do you think that your child is functioning:

- ☐ At the level expected for his/her age?
- ☐ Somewhat behind the level expected for his/her age?
- ☐ Significantly behind the level expected for his/her age?

SECTION 2:

2.1 The next questions ask about your interaction with your child's neurologist. Please think about your child's most recent visit to his/her neurologist for epilepsy care and circle the response that best represents your opinion.

a. To what extent was your child's main problem(s) discussed at that visit?

Completely Mostly A little Not at all

b. Would you say that your doctor knew that this was one of your reasons for coming in for that visit?

Yes Probably Unsure No

c. To what extent did the doctor understand the importance of your reason for coming in for that visit?

Completely Mostly A little Not at all

d. How well do you think your doctor understood you at that visit?

Very well Well Somewhat Not at all

e. How satisfied were you with the discussion of your child's problem?

Very satisfied Satisfied Somewhat satisfied Not satisfied

f. To what extent did the doctor explain this problem to you?

Completely Mostly A little Not at all

g. To what extent did you agree with the doctor's opinion about the problem?

Completely Mostly A little Not at all

h. How much opportunity did you have to ask your questions?

Very much A fair amount A little Not at all

i. To what extent did the doctor ask about your goals for your child's treatment?

Completely Mostly A little Not at all

j. To what extent did the doctor explain treatment?

Very well Well Somewhat Not at all

k. To what extent did the doctor explore how manageable this (treatment) would be for your child and you? He/she explored this:

Completely Mostly A little Not at all

l. To what extent did you and the doctor discuss your respective roles? (Who is responsible for making decisions and who is responsible for what aspects of your child's care?)

Completely Mostly A little Not at all

m. To what extent did the doctor encourage you to take the role you wanted in your child's care?

Completely Mostly A little Not at all

n. How much would you say that this doctor cares about your child as a person?

Very much A fair amount A little Not at all

SECTION 3:

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

SECTION 4:

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

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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
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

Did the change happen in your family:	During the Last 12 Months Yes	No	Score
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

SECTION 5:

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

SECTION 6:

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

SECTION 7:

We would like to understand and measure the experiences of parents who have a child with epilepsy. In particular we wish to know about your perceptions of the care you have been receiving over the past year from the health care institution(s) that provide(s) services to your child for his/her epilepsy.

The care that you and your child receive from this organization may bring you into contact with many individuals. The questions on this form are grouped by who these contacts are, as described below.

PEOPLE:
refers to those individuals who work directly with you or your child. These **may include** doctors, nurses, psychologists, therapists, social workers, etc.

ORGANIZATION:
refers to all staff from the health care institution(s), whether involved directly with your child or not. In addition to health care people they **may include** support staff such as office staff, housekeepers, administrative personnel, etc.

The questions are based on what parents, like yourself, have told us about the way care is sometimes offered. We are interested in your personal thoughts and would appreciate your completing this questionnaire on your own without discussing it with anyone.

7.1. For each question, please indicate how much the event or situation happens to you. You are asked to respond by circling **one** number from 1 (Not at All) to 7 (To a Very Great Extent) that you feel best fits your experience. Please note that the zero value (0) is used only if the situation described does not apply to you.

7. To a Very Great Extent
6. To a Great Extent
5. To a Fairly Great Extent
4. To a Moderate Extent
3. To a Small Extent
2. To a Very Small Extent
1. Not at All
0. Not Applicable

Indicate how much this event or situation happens to you.

IN THE PAST YEAR TO WHAT EXTENT DO THE **PEOPLE** WHO WORK WITH YOUR CHILD	To a Very Great Extent	To a Great Extent	To a Fairly Great Extent	To a Moderate Extent	To a Small Extent	To a Very Small Extent	Not at All	Not Applicable
a. help you to feel competent as a parent?	7	6	5	4	3	2	1	0
b. provide you with written information about what your child is doing in treatment?	7	6	5	4	3	2	1	0
c. provide a caring atmosphere rather than just give you information?	7	6	5	4	3	2	1	0
d. let you choose when to receive information and the type of information you want?	7	6	5	4	3	2	1	0

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IN THE PAST YEAR TO WHAT EXTENT DO THE **PEOPLE** WHO WORK WITH YOUR CHILD	To a Very Great Extent	To a Great Extent	To a Fairly Great Extent	To a Moderate Extent	To a Small Extent	To a Very Small Extent	Not at All	Not Applicable
e. look at the needs of your "whole" child (e.g., at mental, emotional, and social needs) instead of just at physical needs?	7	6	5	4	3	2	1	0
f. make sure that at least one team member is someone who works with you and your family over a long period of time?	7	6	5	4	3	2	1	0
g. fully explain treatment choices to you?	7	6	5	4	3	2	1	0
h. provide opportunities for you to make decisions about treatment?	7	6	5	4	3	2	1	0
i. provide enough time to talk so you don't feel rushed?	7	6	5	4	3	2	1	0
j. plan together so they are all working in the same direction?	7	6	5	4	3	2	1	0
k. treat you as an equal rather than just as the parent of a patient (e.g. by not referring to you as "Mom" or "Dad")?	7	6	5	4	3	2	1	0
l. give you information about your child that is consistent from person to person?	7	6	5	4	3	2	1	0
m. treat you as an individual rather than as a "typical parent" of a child with epilepsy?	7	6	5	4	3	2	1	0
n. provide you with written information about your child's progress?	7	6	5	4	3	2	1	0
o. tell you about the results from assessments?	7	6	5	4	3	2	1	0

IN THE PAST YEAR TO WHAT EXTENT DOES THE **ORGANIZATION** WHERE YOU RECEIVE SERVICES	To a Very Great Extent	To a Great Extent	To a Fairly Great Extent	To a Moderate Extent	To a Small Extent	To a Very Small Extent	Not at All	Not Applicable
p. give you information about the types of services offered at the organization or in your community?	7	6	5	4	3	2	1	0
q. have information available about your child's epilepsy (e.g., its causes, how it progresses, future outlook)?	7	6	5	4	3	2	1	0
r. provide opportunities for the entire family to obtain information?	7	6	5	4	3	2	1	0
s. have information available to you in various forms, such as a booklet, kit, video, etc.?	7	6	5	4	3	2	1	0
t. provide advice on how to get information or to contact other parents (e.g., organization's parent resource library)?	7	6	5	4	3	2	1	0

SECTION 8:

8.1. **In general, would you say your child's health is:** (check one box only)

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

The following questions ask about physical activities your child might do during a day:

8.2. **During the past 4 weeks, has your child been limited in any of the following activities due to health problems?** (check one box on each line)

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Doing things that take **a lot** of energy, such as playing soccer or running?	☐	☐	☐	☐
b. Doing things that take **some** energy, such as riding a bike or skating?	☐	☐	☐	☐
c. Ability (physically) to get around the neighbourhood, playground, or school?	☐	☐	☐	☐
d. Walking one block or climbing one flight of stairs?	☐	☐	☐	☐
e. Bending, lifting or stooping?	☐	☐	☐	☐
f. Taking care of him/herself, that is, eating, dressing, bathing or going to the toilet?	☐	☐	☐	☐

8.3. **During the past 4 weeks, has your child's school work or activities with friends been limited in any of the following ways due to EMOTIONAL difficulties or problems with his/her BEHAVIOUR?** (check one box on each line)

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Limited in the **KIND** of schoolwork or activities with friends he/she could do	☐	☐	☐	☐
b. Limited in the **AMOUNT** of time he/she could spend on schoolwork or activities with friends	☐	☐	☐	☐
c. Limited in **PERFORMING** schoolwork or activities with friends (it took extra effort)	☐	☐	☐	☐

8.4. **During the <u>past 4 weeks</u>, has your child's school work or activities with friends been limited in any of the following ways due to problems with his/her PHYSICAL health?** (check one box on each line)

	Yes, limited A lot	Yes, limited some	Yes, limited a little	No, not limited
a. Limited in the **KIND** of schoolwork or activities with friends he/she could do	☐	☐	☐	☐
b. Limited in the **AMOUNT** of time he/she could spend on schoolwork or activities with friends	☐	☐	☐	☐

8.5. **During the <u>past 4 weeks</u>, how <u>much</u> bodily pain or discomfort has your child had?** (check one box only)

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

8.6. **During the <u>past 4 weeks</u>, how <u>often</u> has your child had bodily pain or discomfort?** (check one box only)

☐ None of the time ☐ Once or twice ☐ A few times ☐ Fairly Often ☐ Very often ☐ Every/almost every day

Below is a list of items that describe chidren's behaviour or problems they sometimes have.

8.7. **How often during the <u>past 4 weeks</u> did each of the following statements describe your child?** (check one box on each line)

	Very Often	Fairly often	Some-times	Almost Never	Never
a. Argues a lot	☐	☐	☐	☐	☐
b. Has difficulty concentrating or paying attention	☐	☐	☐	☐	☐
c. Lied or cheated	☐	☐	☐	☐	☐
d. Stole things inside or outside the home	☐	☐	☐	☐	☐
e. Had tantrums or a hot temper	☐	☐	☐	☐	☐

8.8. **Compared to other children your child's age, in general would you say his/her behaviour is:** (check one only)

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

The following phrases are about children's moods.

8.9. **During the past 4 weeks, how much of the time did your child:** (check one box on each line)

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a.	Felt like crying?	☐	☐	☐	☐	☐
b.	Felt lonely?	☐	☐	☐	☐	☐
c.	Acted nervous?	☐	☐	☐	☐	☐
d.	Acted bothered or upset?	☐	☐	☐	☐	☐
e.	Acted cheerful?	☐	☐	☐	☐	☐

The following question asks about your child's satisfaction with self, school, and others. It may be helpful if you keep in mind how other children your child's age might feel about these areas.

8.10. **During the past 4 weeks, how satisfied do you think your child has felt about:** (check one box on each line)

		Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
a.	His/her school ability?	☐	☐	☐	☐	☐
b.	His/her athletic ability?	☐	☐	☐	☐	☐
c.	His/her friendships?	☐	☐	☐	☐	☐
d.	His/her looks/appearance?	☐	☐	☐	☐	☐
e.	His/her life overall?	☐	☐	☐	☐	☐

The following statements are about health in general.

8.11. **How true or false is each of these statements for your child?** (check one box on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. My child seems to be less healthy than other children I know.	☐	☐	☐	☐	☐
b. My child has never been seriously ill.	☐	☐	☐	☐	☐
c. When there is something going around my child usually catches it.	☐	☐	☐	☐	☐
d. I expect my child will have a very healthy life.	☐	☐	☐	☐	☐
e. I worry more about my child's health than other parents worry about their children's health.	☐	☐	☐	☐	☐

8.12. **Compared to one year ago, how would you rate your child's health now?** (check one box only)

☐	☐	☐	☐	☐
Much better now than 1 year ago	Somewhat better now than 1 year ago	About the same now as 1 year ago	Somewhat worse now than 1 year ago	Much worse now than 1 year ago

8.13. **During the <u>past 4 weeks</u>, how MUCH emotional worry or concern did each of the following cause YOU?** (check one box on each line)

	None at all	A little bit	Some	Quite a bit	A lot
a. Your child's physical health	☐	☐	☐	☐	☐
b. Your child's emotional well-being or behaviour	☐	☐	☐	☐	☐
c. Your child's attention or learning abilities	☐	☐	☐	☐	☐

8.14. **During the <u>past 4 weeks</u>, were you LIMITED in the amount of time YOU had for your own needs because of?** (check one box on each line)

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Your child's physical health	☐	☐	☐	☐
b. Your child's emotional well-being or behaviour	☐	☐	☐	☐
c. Your child's attention or learning abilities	☐	☐	☐	☐

8.15. **During the past 4 weeks, how often has your child's health or behaviour:**
(check one box on each line)

	Very often	Fairly often	Some-times	Almost never	Never
a. limited the types of activities you could do as a family?	☐	☐	☐	☐	☐
b. interrupted various everyday family activities (eating meals, watching tv)?	☐	☐	☐	☐	☐
c. limited your ability as a family to "pick up and go" on a moment's notice?	☐	☐	☐	☐	☐
d. caused tension or conflict in your home?	☐	☐	☐	☐	☐
e. been a source of disagreements or arguments in your family?	☐	☐	☐	☐	☐
f. caused you to cancel or change plans (personal or work) at the last minute?	☐	☐	☐	☐	☐

8.16. **Sometimes families may have difficulty getting along with one another. They do not always agree and they may get angry. In general, how would you rate your family's ability to get along with one another?** (check one box only)

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

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

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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:**

☐☐ / ☐☐ / ☐☐
DAY MONTH YEAR

Thank you for participating in this study.

If there are any other issues concerning your child's health and quality of life that we did not ask but that you would like us to know about, please feel free to mention them below.

Study I.D _ _ _ _

PHYSICIAN FORM

Health Related Quality of Life in Children with Epilepsy:
The First Two Years After Diagnosis Through Parents' Eyes

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): _____
2. Date form completed (dd/mm/yy): _____
3. Seizure type(s): _____ _____
   _____ _____
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: _____

PLEASE TURN OVER TO COMPLETE

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 one 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 one box 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							

Appendix E

Data Analysis

Introduction

Data analysis was conducted with Statistical Analysis Software (SAS 9.1.3 Service Pack 4, SAS Institute Inc., Cary, NC). All hypothesis tests were two-sided with a type I error rate of α=0.05. Univariable analysis was used to describe the sample at each measurement occasion (baseline, and 6, 12, 24 months) in terms of maternal, child, and family factors using descriptive statistics, frequency distributions, and missing data (Appendix F). Examination of attrition on study results was also conducted (Appendix F). Since subjects were recruited from neurologists' clinics, clustering effects within recruitment site were examined to ensure that analytic models presented unbiased estimates (Appendix G). Variables included in analytic models underwent diagnostic testing to identify issues such as the presence of outliers and influence that could potentially bias results (Appendix I). Potential confounding variables were also investigated (Appendix J).

Longitudinal data are central to studying change in outcomes. There are several statistical techniques that can be employed to analyze longitudinal data.[1] One such approach is to examine raw change scores computed as the difference between scores at two different measurement occasions and analyzed as a function of individual or group characteristics.[2] Student *t*-tests, analysis of variance (ANOVA), or multiple regression are generally used to analyze raw change scores. Alternatively, residualized change scores can also be used to study longitudinal data. In this approach, change is calculated as the residual between the observed Time 2 score and the expected Time 2 score as predicted by the score at Time 1.[2] Residualized change scores are typically analyzed with multiple regression or analysis of covariance (ANCOVA). Although both techniques can be useful under specific circumstances of longitudinal data, their use usually results in efficiency loss

as a result of not using all relevant data, bias from selectively omitting or ignoring data, and over-simplification of conclusions and inferences surrounding the research question.[1]

Frequently, researchers are interested in modeling patterns of change in an outcome over multiple (i.e., ≥3) measurement occasions. For example, describing the course of psychopathologies such as depression,[3] understanding criminal behaviour over the life course,[4] educational achievement in children and adolescents,[5] and the impact of medical intervention on the disease progression.[6] One common approach to studying these patterns, or developmental trajectories, is to use latent class growth modeling. As developed by Nagin,[7] latent class growth modeling is a semi-parametric analytic approach to identify subgroups of individuals that follow a similar trajectory in a given sample. The distribution of individual differences of change is summarized using mixtures of appropriately defined probability distributions, each corresponding to a unique trajectory. In other words, this group-based approach assumes that the population under study is composed of a mixture of discrete subgroups defined by their developmental trajectory. Unlike individual growth curve models, this technique fixes the intercept and slope within each trajectory, allowing for an additional degree of freedom to estimate higher-order terms (i.e., quadratic, cubic) for the time variable (Note that individual growth curve modeling can also accommodate fixed intercepts and slopes). Latent class growth modeling can also incorporate both time-varying and time-invariant covariates in order to delineate their effects on the shape and proportion of individuals of a specific trajectory.

Individual growth curve modeling[8] or structural equation/latent growth curve modeling is a second approach to studying patterns of change over time.[9] These techniques use a measure of time (e.g., age, months since diagnosis) as an independent variable to estimate the magnitude and direction of a single trajectory that averages all individual trajectories for an entire sample. Individual differences are captured by estimating a random coefficient that represents the variability

around the averaged intercept and slope. Flexibility in this technique allows researchers to model additional time-varying or time-invariant covariates representing potential risk factors that predict inter-individual differences in intercepts and slopes. In addition, by centering the time variable, the intercept can be set to any predetermined value of interest.

Individual growth curve modeling is generally most useful for investigating research questions in which all individuals are hypothesized to change in a homogeneous trajectory over time, with the magnitude of change being the only source of inter-individual variation in a given sample.[10] However, some phenomena, such as depressive symptomatology, may exhibit a multinomial pattern whereby inter-individual variation may exist in both the magnitude and direction of change.[3, 7, 10] In such circumstances individual growth curve modeling can mask significant differences and lead to erroneous inferences about changes in population over time. Research questions such as these require alternative modeling strategies that consider potential multinomial heterogeneity in change over time, such as latent class growth modeling. The next two sections describe the two most common approaches to modeling patterns of change in an outcome over multiple measurement occasions.

Overview of Latent Class Growth Modeling

Given the substantial contribution of Nagin to both the theory and methodology of latent class growth modeling, the following discussion of this analytic technique draws primarily from his work and from the work of his collaborators.[7, 11] Latent class growth models have two defining features: 1) the predicted trajectory of each group; and 2) the probability that a randomly chosen individual from the sample is a member of each group. Technically, this approach is an application of finite mixture modeling, since it involves combining a mixture of single-group models within the common multiple-group structure.

Using maximum likelihood estimation, the aim of latent class growth modeling is to identify groups of individuals with similar trajectories. The underlying likelihood function, $Y_i = \{y_{i1}, y_{i2}, y_{iT}\}$ denotes a longitudinal sequence of measurements on individual i over T periods. The objective is to estimate a set of parameters that maximizes the probability of Y_i, $P(Y_i)$. For continuous data, $P(Y_i)$ is specified as the censored normal distribution (which is also used for continuous data without censoring). It is assumed that individual differences in trajectories can be summarized by a finite set of different polynomial functions of time. Each set corresponds to a trajectory group denoted by j. $P^j(Y_i)$ denotes the probability of Y_i given membership in group j, and π_j denotes the probability of a randomly chosen individual belonging to group j. However, since group membership is not observed, the proportion of the population comprising each group j, π_j, is an important parameter of interest. Thus, the likelihood function requires aggregation of the J conditional likelihood functions, $P^j(Y_i)$, to form the unconditional probability of the data, Y_i:

$$P(Y_i) = \sum_{j}^{J} \pi_j P^j(Y_i)$$

This equation describes a finite mixture model, because it sums across a finite number of groups that compose the population under study. The term “mixture” is included since the model specifies that the population is composed of a mixture of unobserved groups. Terms in the model include: $P(Y_i)$, the unconditional probability of observing individual i’s longitudinal sequence of measurements; Y_i. It equals the sum across the J groups of the probability of Y_i given i’s membership in group j weighted by the probability of membership in group j, π_j.

The general form of the model as shown in the above equation can be adapted to estimate trajectory models where y_{it} is a censored variable, in which there are clusters of data at the scale maximum or minimum. For example, top students have

grade point averages that cluster at the maximum grade point or individuals may have a score of zero on a measure of number of depressive symptoms. In addition, this model can also be used to model data that are continuous without censoring, such as body mass index.

Adaptation of the general model to censored data requires two important assumptions: 1) choice of an appropriate form of $P^j(y_{it})$ for characterizing the distributional properties of censored data; and, 2) specification of a link function that connects the course of the outcome with time. For censored data, the censored normal distribution is used to define $P^j(Y_i)$ and the linkage between time and the outcome is established via the latent variable, y_{it}^*, which can be conceptualized as measuring individual *i*'s potential for the outcome at time *t*. The censored normal model is described as:

$$y_{it}^* = \beta_0^j + \beta_1^j t_{it} + \beta_0^j t_{it}^2 + \beta_0^j t_{it}^3 + \varepsilon_{ij}$$

where t, t^2, t^3, are linear, quadratic, and cubic measures of time (e.g., age, months since diagnosis), for individual i, respectively, ε_{it} is the random error on each measurement assumed to be normally distributed with mean zero and standard deviation σ, j represents the trajectory group, β_0^j is the parameter that determines the intercept and β_1^j, β_2^j, β_3^j are the parameters that determine the shape of the trajectory. In this model, the latent variable, y_{it}^*, is linked to its censored, but observed counterpart, y_{it}, as follows: If y_{it}^* is less than the minimum value on the outcome scale, y_{it} = MIN and if y_{it}^* is greater than the maximum, y_{it} = MAX. Only when MIN ≤ y_{it}^* ≤ MAX does y_{it}= y_{it}^*.

During the model building process it is important to have *a priori* knowledge of the number and shape of trajectories, whenever theory or empirical findings exist in the research area. Interpretation and comparison of the Bayesian Information Criterion (BIC) is used to guide selection of the most appropriate model that fits the data.

Raftery has argued in favour of the BIC when choosing the number of groups in a mixture model.[12] Nested models examining different numbers of trajectories can be compared using an estimate of the log Bayes Factor [i.e., $2\log_e(B_{10}) \approx 2(\Delta BIC)$], as defined by Jones et al.[13] Both time-varying and time-invariant predictors of group membership can be incorporated into the censored normal model and tested for statistical significance using procedures described by Nagin.[7]

Overview of Individual Growth Curve Modeling

Individual growth curve modeling is another analytic method that allows researchers to measure change over time in a phenomenon of interest (e.g., change in child health-related quality of life) at both the population and individual levels.[8] Other names for this class of statistical methods include random regression models,[14] hierarchical linear models,[15] mixed models,[16] and multilevel models.[17] A convenient way to conceptualize individual growth curve modeling is to consider two levels of analysis as given by the equations below following the notation used by Singer and Willett.[8]

Level 1 model: $$Y_{ij} = \pi_{0i} + \pi_{1i}(t_{ij}) + \varepsilon_{ij}$$

Level 2 model: $$\pi_{0i} = \gamma_{00} + \gamma_{01}(v_i) + \delta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{11}(v_i) + \delta_{1i}$$

The level 1 model is commonly referred to as the intra-individual change model; it captures individual-specific growth rates (Table E.1). The level 2 model is commonly referred to as the inter-individual change model; it captures between-individual variability in the growth rates (Table E.2). In other words, the level 1 model is specified to describe the trajectory of individual change and the level 2 model is specified to represent the relationships between the shapes of individual trajectories and predictors of change.[18] In these equations, t_{ij} and v_i are independent

variables whereby t_{ij} represents the value of time and v_i represents some covariate (e.g., gender). Subscript *i* denotes the individual the observation was made on and *j* denotes the measurement occasion. Since *y* and *t* can carry both *i* and *j* subscripts, both the outcome and time variable are allowed to vary by individuals and occasions. When v_i is absent, the growth model is considered unconditional, since the estimates are not conditional on other covariates in the model.

The structural component of the level 1 model, representing the dependence of true status on time includes the following parameters: $\pi_{0i} + \pi_{1i}(t_{ij})$. The random error that accumulates on each measurement is denoted by the error term, ε_{ij}. Upon inspection, the level 1 model resembles a basic ordinary least squares regression model. The level 1 residuals assumed to be normally distributed with a mean of zero and common variance σ_{ε}^2 and are conditionally independent, given the random effects. However, the marked feature of the level 1 model that differentiates it from the basic regression model is that both the intercept and slope parameters are not fixed, but allowed to vary across individuals. Although the level 1 model has only a single predictor (i.e., t_{ij}), additional time-varying covariates can be included (e.g., family functioning), further reflecting the flexibility of the method.

In the level 2 model, it is helpful to conceptualize the parameter estimates from the level 1 model as outcomes. For example, the intercept of individual *i,* π_{0i}, is written as a function of the population intercept γ_{00}, plus his/her deviation from the population intercept δ_{0i}. The same holds for the slope. In the level 2 model, the population-level estimates (i.e., γ_{00}, γ_{01}, γ_{10}, and γ_{11}) are referred to as the fixed effects. Similar to the basic regression model, these effects are assumed fixed for all individuals. The individual deviations (i.e., δ_{0i} and δ_{1i}), which can be thought of as the level 2 residuals, are referred to as the random effects. The random effects are assumed to be bivariate normally distributed with means of zero and population variance σ_0^2 for the intercept, population variance σ_1^2 for the slope, and population covariance σ_{01}. It is the estimation of the deviations of individuals from the

population curve that puts the "individual" in individual growth curve modeling. The mixture of fixed and random effects in a single model gives rise to other names for this analytic method such as, random coefficient models.[19] An early task in individual growth curve modeling is establishing whether variability associated with the random effects in the growth curves is present. If there is significant variability, the level 2 model can be expanded to include time-invariant risk factors of variability in the individual growth curves (e.g., gender). Testing of main, moderated, and mediated effects in individual growth curve modeling can be implemented following the guidelines of Delucia and Pitts,[20] Aiken and West,[21] and MacKinnon,[22] respectively.

Modeling Assumptions

Evaluating the tenability of individual growth curve modeling assumptions (i.e., functional form, normality, homoscedasticity) followed the guidelines suggested by Singer and Willett.[8] Results of analyses evaluating modeling assumptions are shown in Appendix H. It was assumed that individual change trajectories and relationships between individual growth parameters and level 2 predictors were linear. A direct way of examining the functional form assumption in an individual growth curve model is to inspect level 1 and level 2 plots of the outcome and predictors. At level 1, ordinary least squares-estimated individual growth trajectories were superimposed on empirical growth plots for all individuals. At level 2, ordinary least squares estimates of the individual growth parameters were plotted against each level 2 predictor. With respect to normality, it was assumed that all residuals (at both level 1 and level 2) were normally distributed. Exploratory analyses of the raw residuals were conducted to assess normality. For each residual, a normal probability plot of their values against their associated normal scores was examined, as well as frequency distributions of residual values. Departures from linearity on the normal probability plot indicate a departure from normality. Plots of standardized residuals against predictors were also used to provide insight into the tenability of the normality assumption. That is, if the raw residuals are normally distributed, then

approximately 95% of the standardized residuals will fall within ±2 standard deviations of their center. Plots of standardized residuals by individuals were used to identify outliers in the data. It was assumed that there are equal variances of the level 1 and level 2 residuals at each level of every predictor (homoscedasticity). The homoscedasticity assumption was examined by plotting raw residuals against predictors at each level (i.e., level 1 residuals vs. level 1 predictors). Homoscedasticity holds if the residual variability is approximately equal at every predictor value.

Advantages of Growth Curve Modeling Compared to Traditional Methods

As mentioned previously, relative to traditional methods for analyzing longitudinal data, growth curve modeling offers several advantages. First, ANOVA (i.e., repeated measures ANOVA for longitudinal data) generally focuses on growth curves at the population level. Although ANOVA does allow individual variability in intercepts, individual variability in slopes is not explicitly modeled.[14, 23] That is, the rate of linear change is assumed to be equal for all individuals under study, which under developmental theory is often unrealistic. In growth curve modeling, data are truly modeled at the individual level, allowing for the examination of individual variability in both intercepts and slopes in the phenomenon under study.

Second, the growth curve modeling approach offers researchers greater flexibility in its treatment of the time variable compared to ANOVA. That is, time can be treated continuously rather than as a factor with a finite number of levels and individuals can be observed at different measurement occasions with growth curve modeling with unequal intervals between measurement occasions.[18, 20] In contrast, ANOVA assumes that all individuals were measured on the same occasions and complications arise in analysis when the interval between occasions varies.[24]

A third strength of growth curve modeling is that individuals with missing data at random can be retained in the analysis. Although ANOVA models can incorporate

individuals with partial missing data, researchers often utilize listwise deletion when missing data are encountered, thus potentially resulting in substantial loss of information and can introduce bias into the analysis.[14, 24-26]

Fourth, ANOVA is grounded in a generally untenable assumption of compound symmetry, that repeated measurements are equally correlated over time with constant variance and covariance.[14] This is a far too restrictive assumption since, measurements taken closer together are generally more highly correlated than measurements taken further apart. Adjustments to significance testing to account for violation of this assumption have resulted in considerable sacrifices in statistical power. Growth curve modeling allows flexibility in modeling the covariance structure and thus provides more accurate estimates while maintaining statistical power with relatively smaller sample sizes.[1]

Other advantages of growth curve modeling include the ability to increase the precision of estimates by incorporating an unlimited number of data collection occasions and the ability to model change as linear, curvilinear, or even discontinuous or piecewise function where there may be a "jump" in the growth trajectory at a specific measurement occasion.[18]

Important Considerations in Growth Curve Modeling

Growth curve modeling is deeply rooted in statistical theory. Thus, researchers implementing growth curve modeling must be aware of the conditions that constrain its application. Like most other statistical methods, growth curve modeling was developed on asymptotic theory and as a result may not be appropriate for studies with a small sample size.[1, 14, 15, 20, 27] Use of growth curve modeling in relatively small study samples can lead to systematic errors or bias in parameter estimates.[14] Sample size considerations must account for both the intra- and inter-individual correlations that occur in multilevel studies by applying a design effect to formal sample size calculations based simple random sampling.[28]

The design effect incorporates the intraclass correlation coefficient and thus inflates the sample required to maintain statistical power and provide unbiased estimates as compared to single-level studies.

Also, in growth curve modeling, both the outcome and growth parameters are assumed to be normally distributed.[14, 15] Deviations from normality can introduce bias into the estimates of parameters. If the normality assumption is violated, researchers must utilize any one of a number of transformations (e.g., Box-Cox power transformation, natural logarithm) in order to generate valid results.[1, 29, 30] Due to the fact that levels of depressive symptoms generally exhibit positive skewness, it was anticipated that a natural logarithm transformation would have been required to satisfy the normality assumption.[31, 32] However, plots shown in Appendix H show that the residuals are normally distributed in this study, thus no transformation was required for analysis.

Furthermore, all time-varying variables (i.e., predictors and outcome) should be measured equitably across all measurement occasions when implementing growth curve modeling.[15, 33] The pilot phase of a study is when measurement modification is to be undertaken and not during data collection. Although researchers may be tempted to alter measures, especially during a long study with many intervals of data collection, the so-called "conditioning effects" observed in longitudinal studies are negligible compared to the consequences of modifying measurement instruments.[34, 35] In HERQULES, which is the data source for this study, no modification to the measurement instruments occurred during data collection.

A final consideration in using growth curve modeling considers the number of measurement occasions. At a minimum, researchers must have at least one more measurement occasion than unknown parameters in the level 1 model.[33] For example, in the level 1 model, there are two unknown parameters, the intercept, π_{0i} and slope, π_{1i}, thus at least three measurement occasions are required. This is

because with three measurement occasions, there remains one degree of freedom. If only two measurement occasions were completed, the model would be considered saturated and there would be no degrees of freedom; a straight line would connect both measurement occasions. Continuing with this logic, if a researcher wanted to include a third parameter in level 1 to model a quadratic function of time (i.e., π_{2i}), four measurement occasions would be required. The number of measurement occasions must be critically examined prior to implementing a longitudinal study, since feasibility issues may constrain subsequent analyses. HERQULES included four measurement occasions which permitted modeling of non-linear change over time.

Data Analysis

Objective: Informant Bias

Determine if mothers of children with new-onset epilepsy exhibiting depressive symptoms provide bias reports of child outcomes.

In order to address limitations associated with dichotomizing mothers as depressed or non-depressed described by Richters and to ensure that results were not an artifact based on other extraneous variables, moderation was assessed using product terms in multiple regression analyses.[36] Fifteen regression models were conducted whereby the mothers' report was the dependent variable [e.g., Quality of Life in Childhood Epilepsy (QOLCE) (total)] and was regressed on the neurologists' report [e.g., Global Assessment of Severity of Epilepsy (GASE)], mothers' depressive symptoms (Center for Epidemiological Studies Depression Scale, CES-D), and an interaction term conceptualized as the product between neurologists' report and mothers' depressive symptoms (i.e., GASE×CES-D). The product term is included to determine whether the relationship between the mother report and the neurologist report is moderated by the mother's mental health status. A statistically significant product term indicates that mothers with lower versus higher levels of depressive

symptoms differ in the extent to which their reports are similar to neurologists' reports.

For the functional status domain, the cognition subscale of the QOLCE was regressed on a five-point (higher scores indicate better functioning) neurologist assessment of child cognitive problems. As well, the QOLCE subscales physical restrictions and energy/fatigue and the CHQ subscales role-physical and physical functioning were regressed on a seven-point neurologist assessment of interference of epilepsy or treatment with daily activities (higher scores indicating fewer disruptions). For psychological functioning, the behavior subscale of the QOLCE and the role-emotional/behavior and behavior subscales of the CHQ were regressed on a four-point (higher scores indicate better functioning) neurologist assessment of child behavior problems. To assess social functioning, the QOLCE subscales social interactions, social activities and stigma were regressed on the neurologist assessment of interference of epilepsy or treatment with daily activities. In terms of disease state/symptoms, mother-reported overall QOLCE and CHQ (physical and psychosocial) summary scores were regressed on the neurologist-reported GASE (higher scores indicate less severity).

In the presence of a statistically significant product term, a conditional moderator variable based on CES-D scores and the standard deviation of the sample was used in subsequent *post hoc* regression analyses as described by Holmbeck to probe interactions and further describe the effect of mothers' depressive symptoms on their reports.[37] Briefly, high and low maternal depressive symptoms conditional moderator variables are created by adding (HIGH_CESD) and subtracting (LOW_CESD) the standard deviation from the mean CES-D score. New interaction terms are computed by multiplying the neurologists' report (NEURO) and the conditional moderator (i.e., HIGH_INT = NEURO × HIGH_CESD and LOW_INT = NEURO × LOW_CESD). Then, two *post hoc* regression models are run, each of which include the NEURO main effect, one of the conditional depressive symptoms moderator (HIGH_CESD or LOW_CESD), and the new interaction (HIGH_INT or

LOW_INT). These regression models generate the slope for both the high depressive symptoms and low depressive symptoms condition. The regression lines can then plotted to visual the effect of depressive symptoms on maternal reports of child health-related quality of life.

Objective: Prevalence and Trajectory

Estimate the prevalence and course of depressive symptoms over 24 months among mothers of children with new-onset epilepsy.

Univariable analyses used to describe maternal depressive symptoms at each measurement occasion included descriptive statistics and frequency distributions. Bivariable analyses (i.e., *t*- and χ^2-tests) were used to compare mothers who completed the 24-month follow-up with those who did not complete the study.

Patterns of self-reported maternal depressive symptoms, as measured by the CES-D, during the first 24 months after having a child diagnosed with epilepsy were investigated with the semi-parametric, group-based approach developed by Nagin.[7, 11] The group-based trajectory model is an example of a latent class model whereby a polynomial function is used to model the relationship between depressive symptoms and time. This approach estimates individual growth trajectories and then identifies prototypical trajectories that best describe the data. The degree to which an individual's trajectory resembles the prototypic trajectory is estimated and individuals are categorized into trajectory groups based on the similarity of the individual trajectory to the prototypic trajectories. A censored normal model was fitted to the data since there were a number of mothers who exhibited no or few depressive symptoms, resulting in a cluster of data at the scale minimum. By accounting for this censoring in specifying the likelihood function, the censored normal model provides consistent estimates of the parameters that describe each trajectory group. The number of groups to be included in the model is guided by *a priori* expectations, overall model fit based on the Bayesian Information Criterion

(BIC), and posterior probability scores for each trajectory group. The model with the maximum BIC, optimized probability scores, and least number of groups is selected. The modeling process followed the strategy of Campbell et al.[3] whereby, cubic trajectories were specified for three groups being examined and in order to ensure parsimony, non-significant higher-order terms (i.e., quadratic and cubic) were removed and the model was respecified until optimal fit was achieved.[38] Additional groups were added to the model and the change in BIC scores examined to determine the best model. The resulting model was considered unconditional since no predictors, other than time (i.e., linear, quadratic, and cubic terms), were included. Latent class growth modeling was conducted with PROC TRAJ as described by Jones et al.[13, 39]

Objective: Risk Factors

Determine the risk factors that predict trajectory group membership among mothers over 24 months.

Maternal, child, and family characteristics were compared across trajectory groups using ANOVA for continuous variables and χ^2-tests for categorical variables. To avoid errors in statistical inference due to multiple testing, the Bonferroni correction ($\alpha/18=0.003$) was applied to hypothesis tests across trajectory groups. Pairwise group contrasts (*post hoc* Scheffé or χ^2-test, when appropriate) were examined only if a statistically significant overall difference was observed across trajectory groups.

Multinomial logistic regression was conducted to identify predictors of trajectory group membership using baseline data. A backward, stepwise selection approach using maternal, child, and family characteristics was utilized. Only variables that were statistically significant in the bivariate comparisons were included in the regression analysis. In order to generate a robust model, the condition for variables

to enter and remain in the model was set at α=0.20.[40] Continuous variables in the model were categorized into quartiles to increase interpretability of the model.

Objective: Causal Modeling

Assess the family factors involved in the causal pathway between maternal depressive symptoms and child health-related quality of life over 24 months.

Individual growth curve modeling was used to examine the impact of maternal depressive symptoms on child HRQL during the 24-month follow-up.[8] Individual growth curve modeling is one of several approaches developed to handle the violation of independence between repeated measures for individuals studied in prospective cohort designs in order to produce robust and unbiased estimates. This approach accounts for the violation of independence by specifying both intra- and inter-individual equations, such that the structure of the data is conceptualized as repeated measures clustered within individuals.[8] Individual growth curve models were analyzed following the guidelines described by Singer, which considered time of assessment (in terms of months since child was diagnosed with epilepsy) and maternal depressive symptoms as time-varying predictors of child health-related quality of life.[41] Both the model intercept and slope were specified as random effects (i.e., differing for each individual in the sample). An unstructured variance-covariance matrix was specified which is the most heterogeneous type and requires estimation of several parameters, thus additional degrees of freedom, but does not constrain any pairwise comparisons within the matrix, allowing for additional flexibility.[1] Variables were centered on their respective sample means at 24 months to improve interpretation of results.

To obtain unbiased estimates of effect, potential confounders were tested *a priori* to the growth curve modeling. Potential confounders tested were maternal age, marital status, employment status, education, parity, child age, child sex, seizure type, age of onset, total number of anti-epileptic drugs, illness severity, behaviour problems,

cognitive disability, motor dysfunction, and family income. Confounding was determined by adding the variable to the model to examine the change in the effect estimate. For the purposes of this study, a collapsibility criterion was used to operationally define confounders as those variables, when entered in the model resulted in a ≥10% change in the effect estimate of maternal depressive symptoms on child health-related quality of life and was thus retained in the model.[42]

Moderation was examined by sequentially testing growth curve models of child health-related quality of life regressed on maternal depressive symptoms in the presence of each potential moderator using a product interaction term. To examine whether family resources or perception of healthcare moderated the impact of maternal depressive symptoms on child health-related quality of life the 24-month follow-up, a two-way interaction between maternal depressive symptoms and the moderator was entered in the model. A three-way interaction between maternal depressive symptoms, the moderator, and time was entered to examine whether the magnitude of the moderating effect varied over time. The moderation analyses conformed to Kleinbaum's Hierarchy Principle such that maternal depressive symptoms and moderator main effects were included in the model assessing the interaction term.[43]

The product of coefficients method described by MacKinnon et al. was used to examine the potential mediating effects of family functioning and family demands on the relationship between maternal depressive symptoms and child health-related quality of life as illustrated in Chapter Five (Figure 5.1).[44] The product of coefficients method has been shown to have more accurate type I error rates and greater statistical power compared to the more traditionally employed causal steps described by Baron and Kenny.[45] Instead, the product of coefficients approach involved estimating two growth curve models:

$$M = c_M + \alpha X + \varepsilon_M$$

$$Y = c_Y + \tau X + \beta M + \varepsilon_Y$$

And then computing the product of $\hat{\alpha}$ and $\hat{\beta}$ to form the mediated or indirect effect. The rationale behind this approach is that mediation is dependent upon the extent to which the predictor impacts the mediator, α, and the extent to which the mediator impacts the outcome, β. The proportion of the total effect that is mediated was calculated using a ratio of the indirect effect, $\widehat{\alpha\beta}$, divided by the total effect, $\widehat{\alpha\beta} + \hat{\tau}$. Significance of the mediated effect was tested by dividing the product by its standard error and compared to the standard normal distribution and by construction of confidence intervals:

$$\alpha\beta \pm Z \times \sqrt{\alpha^2\sigma_\beta^2 + \beta^2\sigma_\alpha^2}$$

The standard error of $\widehat{\alpha\beta}$ was calculated using the method described by Sobel:[46]

$$z = \frac{\alpha\beta}{\sqrt{\alpha^2\sigma_\beta^2 + \beta^2\sigma_\alpha^2}}$$

The Sobel method is the most commonly used approach to calculating the standard error and has been shown to produce unbiased and statistically robust results.[44] Growth curve models used in the mediation analysis were adjusted for potential confounding factors using the methods described by Li et al. in order to obtain unbiased estimates of effect.[47]

Study Power

This study will use HERQULES as its framework for data analysis. At baseline, 339 individuals were enrolled in the study. Due to the novel contribution of this research, there is a lack of prior information required for calculating an appropriate

sample size. Baseline data were used to determine the precision in which the mean score on the CES-D can be estimated. The calculations were based on the square-root transformation of baseline CES-D scores in order to satisfy the assumption of normality.

Since this study implemented growth curve modeling, several pieces of information were required in order to determine the precision of estimates.[28] First, the intraclass correlation coefficient is needed to determine the magnitude of the design effect that will be applied to equation. The intraclass correlation coefficient is given by the following equation:

$$\rho = \frac{MS_B - MS_W}{MS_B + (k-1)MS_W}$$

where, MS_B is the mean squared error between groups; MS_W is the mean squared error within groups; and, k is the mean number of subjects per clinical site

Conducting an ANOVA and substituting into the equation resulted in an intraclass correlation coefficient of ρ=0.017. Next, the design effect introduced by deviating from a simple random sampling strategy was determined with the following equation for multilevel analyses:

$$DEFF = [1 + (n-1)\rho]$$

Substituting values into the equation resulted in a design effect of 1.102. Finally, using estimates of population parameters of CES-D scores from HERQULES (μ=14.6; σ=10.6) and previous studies,[48, 49] the precision of the estimate of mean CES-D score was calculated with the following equation:

$$p = DEFF \times \frac{Z_{1-\alpha/2} \times \sigma}{\sqrt{N} \times \mu}$$

where, $Z_{1-\alpha/2}$ is the level of confidence;
σ is the population standard deviation;
μ is the population mean; and,
N is the number of baseline mothers in HERQULES

Based on the number of individuals participating in HERQULES at baseline, the estimate of maternal depressive symptoms can fall within 3% of the population mean CES-D score.

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Table E.1. Definition and Interpretation of Parameters in the Level 1 Model.

	Symbol	Definition	Illustrative Interpretation
Fixed effects	π_{0i}	Intercept of the true change trajectory for individual *i* in the population	Individual *i*'s true value of child health-related quality of life at time 1 (i.e., true initial status)
	π_{1i}	Slope of the true change trajectory for individual *i* in the population	Individual *i*'s rate of change in true child health-related quality of life (i.e., true rate of change between measurement occasions)
Variance component	σ_{ε}^{2}	Level 1 residual variance across all occasions of measurement, for individual *i* in the population	Summarizes the net (vertical) scatter of the observed data around individual *i*'s hypothesized change trajectory

Adapted from Singer and Willett.[8]

Table E.2. Definition and Interpretation of Parameters in the Level 2 Model.

	Symbol	Definition	Illustrative Interpretation
Fixed effects	γ_{00}	Population average of the level 1 intercepts, π_{0i}, for individuals with a level 2 predictor value of 0	Population average true initial status for females (reference category)
	γ_{01}	Population average difference in level 1 intercept, π_{0i}, for a one-unit difference in the level 2 predictor	Difference in population average true initial status between females and males
	γ_{10}	Population average for the level 1 slopes, π_{1i}, for individuals with a level 2 predictor value of 0	Population average rate of true change for females
	γ_{11}	Population average difference in level 1 slope, π_{1i}, for a one-unit difference in the level 2 predictor	Difference in population average rate of true change between females and males
Variance components	σ_0^2	Level 2 residual variance in true intercept, π_{0i}, across all individuals in the population	Population residual variance of true initial status, controlling for gender
	σ_1^2	Level 2 residual variance in true slope, π_{1i}, across all individuals in the population	Population residual variance of true rate of change, controlling for gender
	σ_{01}	Level 2 residual covariance between true intercept, π_{0i}, and true slope, π_{1i}, across all individuals in the population	Population residual covariance between true initial status and true rate of change, controlling for gender

Adapted from Singer and Willett.[8]

Appendix F

Sample Characteristics and Attrition

Introduction

Measurement occasions were not based on empirical evidence of depressive symptom trajectories; instead data collection was guided by the clinical course of epilepsy and associated follow-up appointments with paediatric neurologists. However, it is believed that the measurement occasions were close enough together to avoid missing potential fluctuations in maternal depressive symptoms and distanced enough to allow for sufficient time to detect important changes. Three assessments were completed in the first 12 months since during this time maternal and family factors and clinical management of epilepsy are hypothesized to be relatively dynamic. In the second year, circumstances are believed to stabilize and thus an assessment at 24 months was deemed appropriate.

Sample Characteristics

Characteristics of the study sample at diagnosis (baseline), and 6, 12, and 24 months are shown in Table F.1. Briefly, mothers were generally married, employed, and had obtained post-secondary education. Children generally had partial seizures, good health-related quality of life, less severe epilepsy. There were approximately equal numbers of males and females and relatively few children had cognitive, behaviour, or motor comorbidities. Families were generally functioning well, had adequate resources, few demands, and had high-income.

Attrition

This study had relatively low attrition with 76% of individuals completing all four measurement occasions. A total of 81 individuals were lost during the follow-up (27

between baseline and six months; 31 between 6 and 12 months; and, 23 between 12 and 24 months). Mothers with higher levels of depressive symptoms and other risk factors for clinical depression[1] were less likely to complete the 24-month follow-up compared to mothers who did not exhibit such traits (Chapter 4). A similar trend has been observed in other research of mothers with depressive symptoms.[2, 3] This is shown in Table F.1 and Figure F.1.

Figure F.1. Examining Attrition in HERQULES. Mothers who did not complete the 24-month follow-up (attrition=1), were observed to have higher scores on the Center for Epidemiological Studies Depression Scale (CES-D).

Using individual growth curve modeling (Appendix E), attrition status was observed to be positively associated with depressive symptoms, but this relationship was negated when controlling for the potential confounding effects of maternal and family characteristics (Table F.2). Bias due to losses during follow-up may under-estimate the proportion of mothers at risk. When baseline characteristics of mothers who did not complete the study were compared to characteristics from

each trajectory group, results showed that those lost during follow-up most closely resembled the *moderate increasing* group (Chapter 4).

References

1. Lehtinen V, Joukamaa M. Epidemiology of depression: prevalence, risk factors and treatment situation. Acta Psychiatr Scand Suppl 1994;377:7-10.

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3. de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000;152:1039-47.

Table F.1. Description of Maternal, Child, and Family Characteristics at each Measurement Occasion during the 24-Month HERQULES Follow-up.

	Baseline	6 Months	12 Months	24 Months
Sample Size	339	312	281	258
Maternal Characteristics				
Age, years	37.7 (5.8)	28.5 (5.7)	39.2 (5.7)	40.4 (5.5)
Marital Status, %				
Not Married	19.8	20.0	19.3	18.1
Married*	80.2	80.0	80.7	81.9
Employment Status, %				
Not Employed	9.5	8.3	4.7	6.6
Employed	66.1	70.2	74.4	77.7
Homemaker	22.9	19.5	18.8	15.2
Student	1.5	2.0	2.2	0.4
Education, %				
Primary School	11.5	8.1	6.5	5.0
High School	20.9	20.6	19.1	19.2
Technical Training	13.6	11.5	13.3	11.9
College/University	54.0	59.8	61.2	63.9
Number of Children	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
Depressive Symptoms, CES-D	14.6 (10.6)	11.7 (9.5)	12.2 (9.7)	12.0 (10.0)
Child Characteristics				
Age, years	7.4 (2.4)	7.9 (2.4)	8.4 (2.4)	9.4 (2.4)
Sex, %				
Male	52.2	51.3	50.9	51.6
Female	47.8	48.7	49.1	48.4
Seizure Type, %				
Generalized	38.6	39.7	39.2	37.3

Partial	61.4	60.3	60.8	62.7
Health-related Quality of Life, QOLCE	70.4 (13.4)	74.0 (13.0)	74.9 (13.4)	75.9 (13.9)
Epilepsy Severity, GASE	5.4 (1.2)	6.0 (1.1)	6.1 (1.1)	6.3 (1.0)
Co-morbidities, %				
Behavior Problems	14.1	21.2	19.1	20.0
Cognitive Problems	13.6	14.1	15.1	17.5
Motor Problems	6.3	6.8	7.7	5.7
Family Characteristics				
Functioning, Family APGAR	14.0 (3.8)	14.1 (3.6)	14.0 (3.9)	14.1 (3.8)
Resources, FIRM	50.1 (11.1)	51.0 (10.9)	50.5 (11.4)	50.7 (11.5)
Demands, FILE	9.6 (6.5)	NM	8.1 (6.1)	7.9 (5.8)
Perception of Patient-centered Care, PPPC	1.6 (0.5)	NM	1.6 (0.6)	1.6 (0.6)
Annual Household Income, %				
< $20,000	7.7	8.5	5.2	4.0
$20,000-39,999	13.5	13.3	13.9	10.0
$40,000-59,999	21.2	19.1	16.9	18.8
$60,000-79,999	18.2	16.4	16.5	18.4
≥ $80,000	37.2	40.6	43.8	44.0
Unknown	2.2	2.1	3.8	4.8

Reported as mean (standard deviation), unless otherwise stated.
NM, not measured.
*Includes mothers in married and common-law relationships.

Table F.2. Growth Models for the Impact of Attrition on Maternal Depressive Symptoms.

	Model A	Model B	Model C
Fixed Effects			
Final Status			
Intercept	12.60 (0.57)*	12.46 (0.56)*	12.20 (0.45)*
Attrition Status	4.41 (1.18)†	3.10 (1.12)‡	0.76 (1.03)§
Age		-0.28 (0.07)†	-0.25 (0.06)*
Education		-1.10 (0.35)‡	-0.87 (0.31)‡
Employment Status		-2.05 (0.49)*	-1.60 (0.51)‡
Marital Status		3.46 (0.92)†	0.83 (0.85)§
Functioning			-0.39 (0.09)*
Resources			0.39 (0.06)*
Demands			-0.28 (0.03)*
Rate of Change			
Time	-0.26 (0.15)§	-0.10 (0.16)§	-0.15 (0.14)§
Variance Components			
Level 1			
Intra-individual	38.54 (2.29)*	38.07 (2.32)*	32.88 (2.30)*
Level 2			
Final Status	56.72 (8.02)*	49.06 (7.43)*	18.38 (5.00)†
Rate of Change	1.64 (0.59)‡	1.49 (0.59)‡	0.44 (0.56)§
Covariance	1.91 (1.73)§	2.44 (1.71)§	-1.22 (1.30)§
Goodness-of-Fit			
Deviance	8364.9	7974.1	5649.0

Values denote β-coefficient (standard error). Model A is the unconditional growth model; Model B is the semi-conditional growth model, controlling for maternal factors (age, education, employment, and marital status); Model C is the fully conditional growth model, controlling for maternal and family factors (functioning, resources, and demands).

*p<0.0001, †p<0.001, ‡p<0.01, §p<0.05

Appendix G

Growth Curve Modeling and Intraclass Correlation

Introduction

As discussed in the methodological details of the study (Appendix A), there is potential for clustering effects that may introduce biased effects estimates if not appropriately accounted for in the analyses. Since subjects were recruited from paediatric neurology clinics across Canada, analyses may require a three-level approach, whereby repeated measures on individuals were clustered at the recruitment site. Thus, there is potential for intra-individual, inter-individual, and inter-site variation that must be addressed.

Intraclass Correlation

If it is the case that a three-level model is correct, clustering effects must be addressed since individuals within clusters are more likely to be similar with respect to the variables of interest compared to those individuals in other clusters.[1] It is this violation of the assumption of independence that can result in biased estimates.[1] The intraclass correlation coefficient (ICC) is a measure of the degree of dependence of individuals and can be used to determine whether clustering effects were present in the data.[2] An equation for the ICC is given as:[3]

$$\rho = \frac{MS_B - MS_W}{MS_B + (k-1)MS_W}$$

where, MS_B is the mean squared error between groups; MS_W is the mean squared error within groups; and, k is the mean number of subjects per clinical site

There are differing views regarding when an ICC is large enough that it must be included in the analyses. Kreft and de Leeuw suggest that an ICC less than 0.1 may

be safely ignored,[2] whereas others such as Barcikowski, note that even a small ICC can have substantial effects on significance tests especially when the number of individuals within a cluster is large.[4] Given the discrepancies highlighted, a formal test of the ICC was conducted using the equation below:[3]

$$F_{g-1,g(k-1)} = \frac{1+(k-1)\rho}{1-\rho}$$

where, k is the mean number of subjects per clinical site; and, g is the number of clinical sites

The ICC was calculated using analysis of variance of maternal depressive symptom scores, based on the Center for Epidemiological Studies Depression scale, across recruitment sites at each measurement occasion. An *F*-test was then used to determine the statistical significance of the ICC.

Table G.1 displays the results of the analysis. Since the calculated *F*-statistics were not more extreme than the critical *F*-value, F^*, the results suggest that no clustering effects at the level of recruitment site were present in the data. In addition, since the number of individuals per cluster was relatively small, the ICCs were ignored for all analyses. As a result, two-levels (level 1, intra-individual; level 2, inter-individual) were used in all analytic models. The violation of independence due to repeated measures on the same individual over time is accounted for with the use of PROC MIXED and PROC TRAJ, resulting in unbiased effect estimates.[5, 6]

References

1. Hox JJ, Kreft IGG. Multilevel analysis methods. Sociol Method Res 1994;22:283-99.

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

3. MacKinnon DP. Introduction to statistical mediation analysis. Hoboken: Erlbaum Psych Press; 2008.

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5. Singer JD. Fitting individual growth models using SAS PROC MIXED. In: Moskowitz DS, Hershberger SL, eds. Modeling intraindividual variability with repeated measures data Methods and applications. Mahwah: Lawrence Erlbaum Associates; 2002.

6. Jones BL, Nagin DS. Advances in group-based trajectory modeling and a SAS procedure for estimating them. Soc Methods Res 2007;35:542-71.

Table G.1. Parameters Involved in Estimating Potential Clustering Effects.

	MS_B	MS_W	k	g	ICC	*F*	F^*
Time 1	113.20	111.02	7	49	0.003	1.02	1.40
Time 2	66.05	91.32	6	49	-0.048	0.73	1.41
Time 3	105.43	98.49	6	49	0.012	1.07	1.41
Time 4	70.46	106.97	5	49	-0.073	0.66	1.42

See text and equations for definitions of abbreviations.

Appendix H

Tenability of Modeling Assumptions[a]

Evaluation of modeling assumptions required for individual growth curve modeling followed the suggestions described by Singer and Willet.[1]

The assumption of functional form (i.e., linearity) was examined by inspecting level 1 and level 2 plots of the outcome and predictors. At level 1, ordinary least squares-estimated individual growth trajectories were superimposed on empirical growth plots of health-related quality of life for all individuals. A random sample of these plots is shown in Figure H.1. The hypothesis of linear individual change seemed reasonable for the subjects shown, except for subject 8406, with which there may be evidence of quadratic change. It is however, difficult to argue for systematic deviation from linearity for this individual given that the departure observed might be attributable to measurement error. Inspection of empirical growth plots for all individuals in the study led to similar conclusions. At level 2, examination of the level 2 assumption of linearity was facilitated by plotting ordinary least squares estimates of the individual growth parameters (i.e., intercept and slope) against the level 2 predictor, maternal depressive symptoms, as measured with the Center for Epidemiological Studies Depression Scale (CES-D). As shown in Figure H.2, the data suggested a strong linear relationship between the individual growth parameters and maternal CES-D scores.

The assumption of normality was explored using normal probability plots at both levels 1 and 2, as well as frequency distribution curves. In addition, plots of standardized level 2 residuals against maternal depressive symptoms were also examined to assess normality. Plots of standardized residuals against subject ID were also examined to identify potential extreme individuals in the data. As shown

[a]Due the number of figures in this Appendix, they are shown sequentially at the end of the Appendix rather than within the text.

in Figures H.3 and H.4, the normal probability plots at levels 1 and 2 appear linear, indicating that the normality assumption was satisfied. This is supported with the histograms in Figures H.5 and H.6 that exhibit normally distributed residuals at levels 1 and 2. Although the normal probability plot for residuals of the level 2 intercepts appeared somewhat bent, individual growth curve modeling is an analytic technique that can handle deviations from normality and still provide robust conclusions.[1] Plots of standardized level 2 residuals against maternal CES-D scores are shown in Figure H.7. These plots provide additional evidence for the normality assumption since approximately 95% of the standardized residuals lie within ±2 standard deviations of their center. Figures H.8 and H.9 show plots of standardized residuals against subject ID. Again, the results appeared to conform to normal theory assumptions since the vast majority lie within ±2 standard deviations of their centers at both level 1 and level 2.

The assumption of homoskedasticity was investigated by plotting level 2 raw residuals against maternal CES-D scores. As shown in Figure H.10, the assumption appeared to hold since residual variation was approximately equal across values of the CES-D for both the intercept and slope.

References

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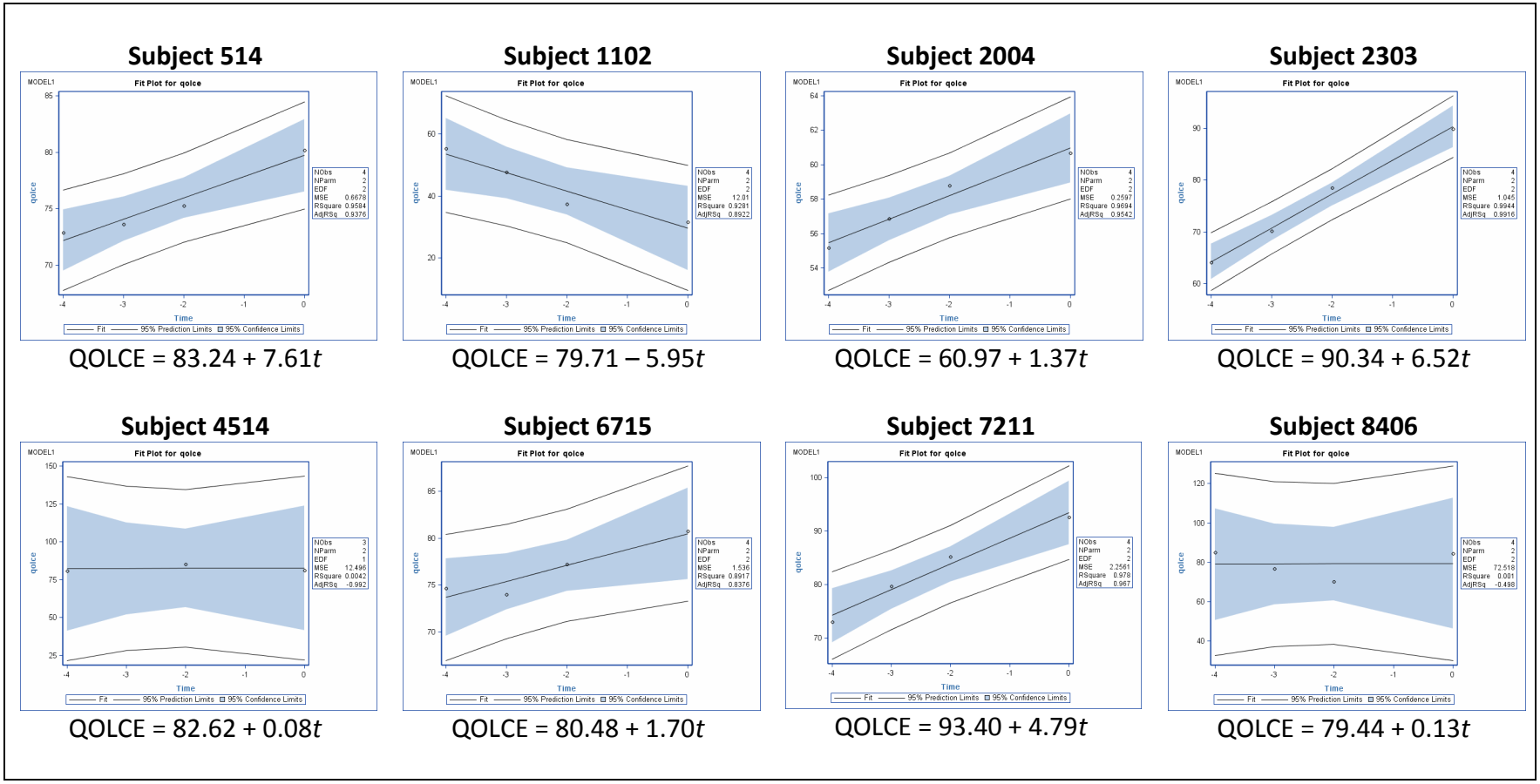

Figure H.1. Examination of the Level 1 Linearity Assumption. A random sample of ordinary least squares-estimated individual growth trajectories were superimposed on empirical growth plots of child health-related quality of life scores, as measured with the Quality of Life in Childhood Epilepsy (QOLCE) over 24 months. The solid line represents a fitted regression trajectory, dotted lines represent the probability that the population trajectory falls between the bands, while the shaded region depicts the 95% confidence intervals.
t, time, centered at 24 months.

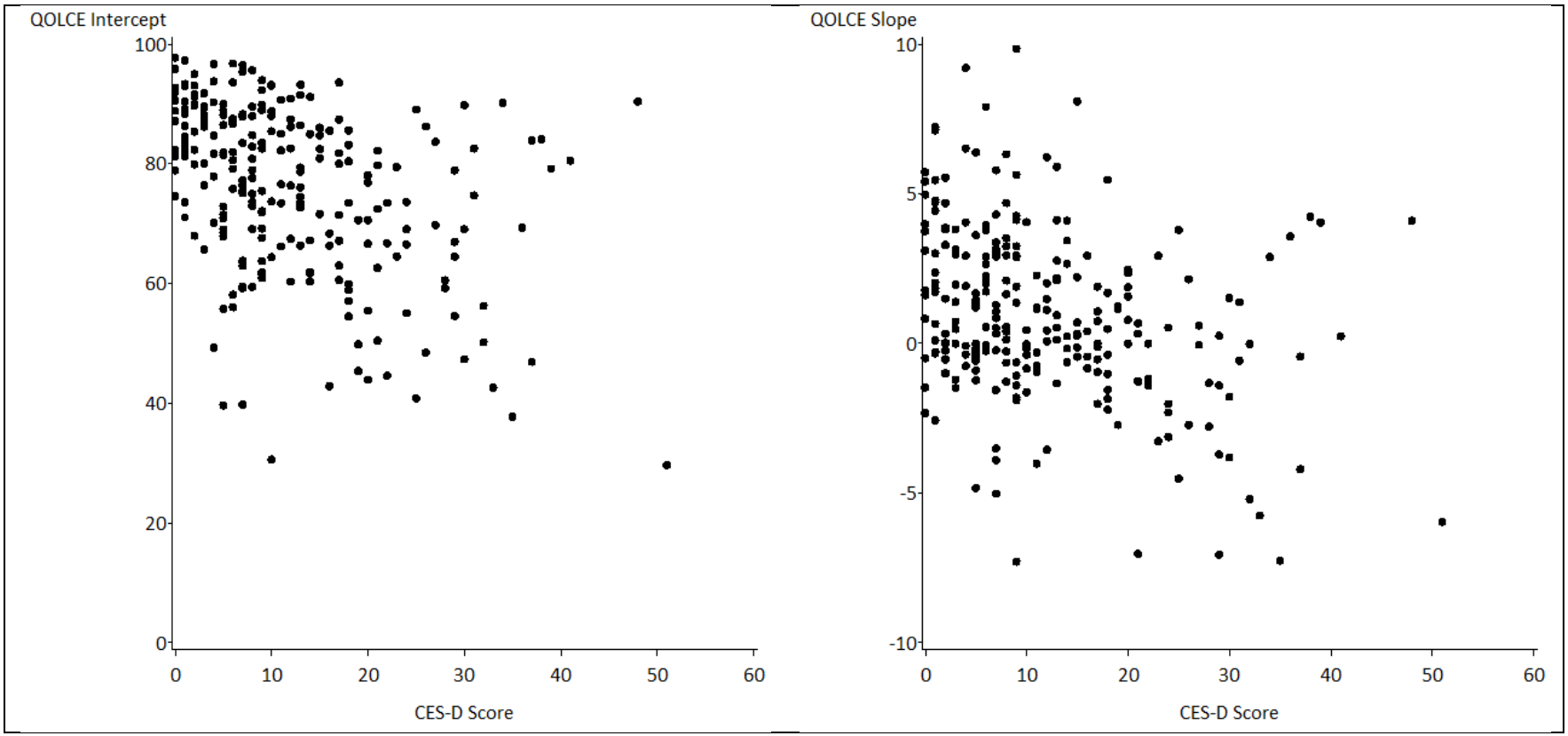

Figure H.2. Examination of the Level 2 Linearity Assumption. Ordinary least squares-estimated individual growth parameters (*left,* intercept; *right,* slope) plotted against the level 2 predictor, maternal CES-D scores. Both plots suggested a strong linear relationship between the QOLCE intercept (r=-0.40, p<0.0001) and slope (r=-0.31, p<0.0001) with maternal CES-D scores. CES-D, Center for Epidemiological Studies Depression Scale; QOLCE, Quality of Life in Childhood Epilepsy.

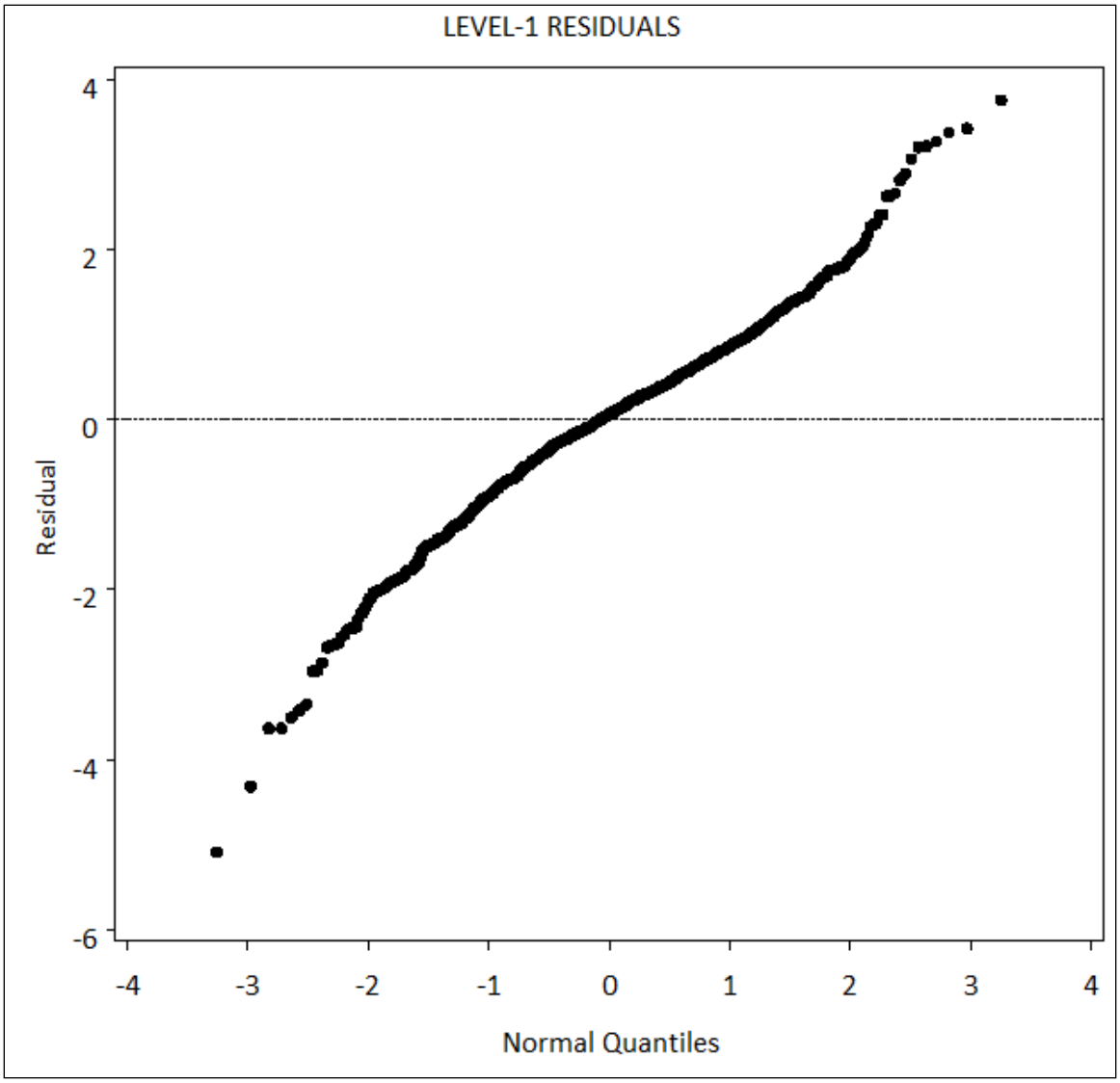

Figure H.3. Level 1 Normal Probability Plot. The "S" shape in the plot suggests that there was slightly more variance than would be expected for completely normally distributed data. However, the linear component of the plot suggests that the normality assumption is satisfied at level 1.

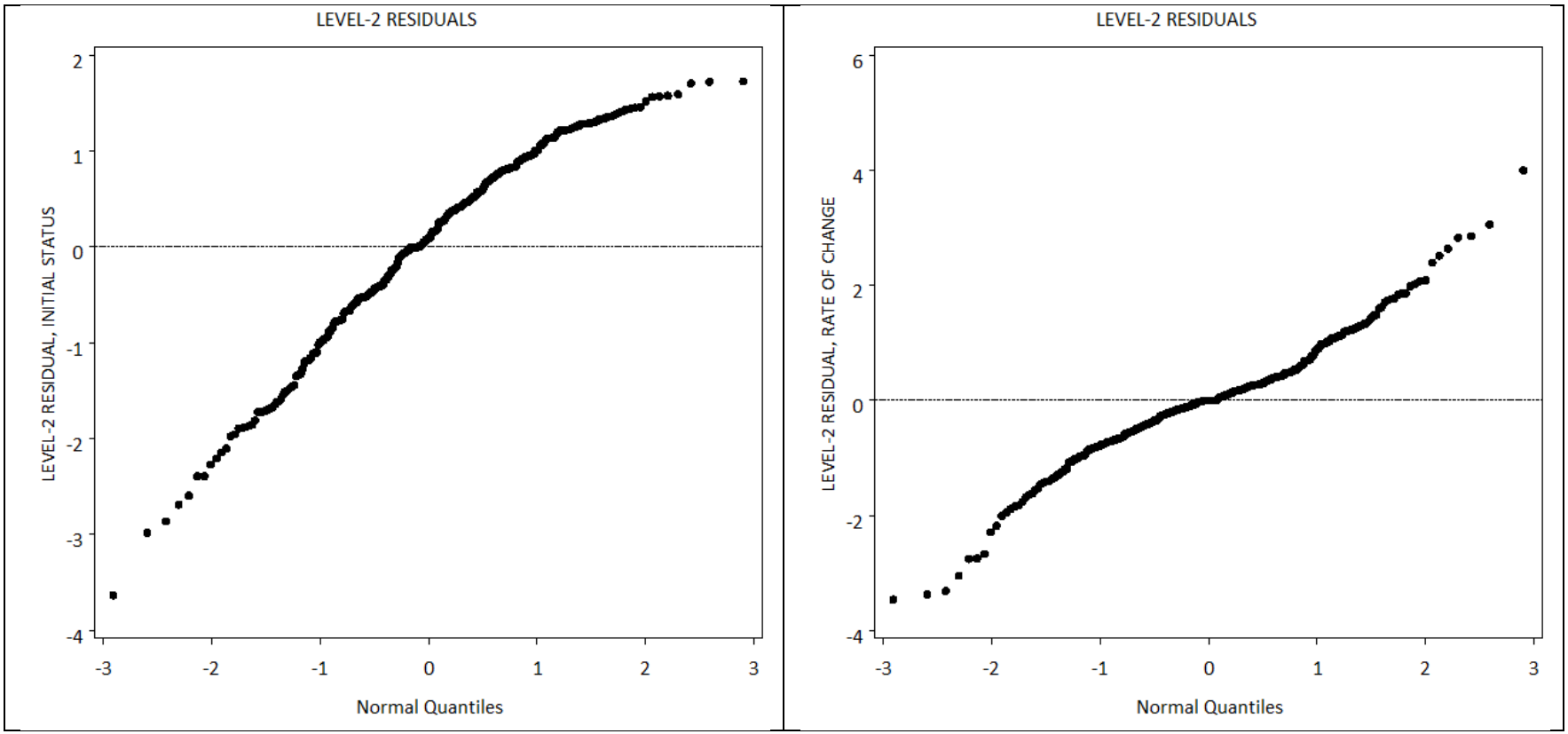

Figure H.4. Level 2 Normal Probability Plots (left, intercept; right, slope). The intercept plot displays a slight bend indicating a left skew in the data (further evidence is shown in Figure H.6) and the slope plot shows a similar shape to the level 1 residual plot. Again, these slight deviations from linearity in the normal probability plot were not extreme enough to violate the normality assumption.

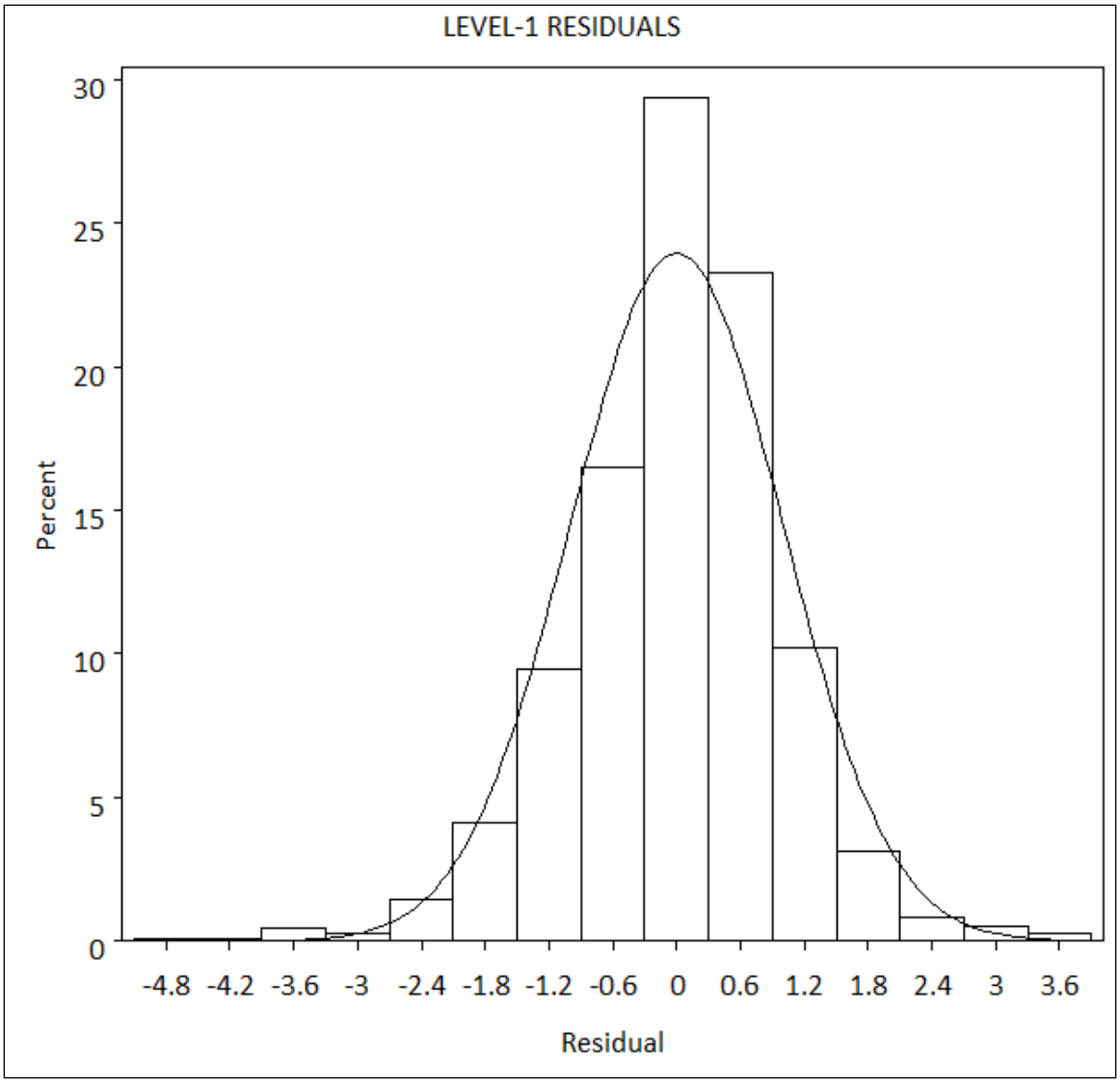

Figure H.5. Histogram of Level 1 Standardized Residuals. As a complement to Figure H.3, level 1 residuals appeared normally distributed.

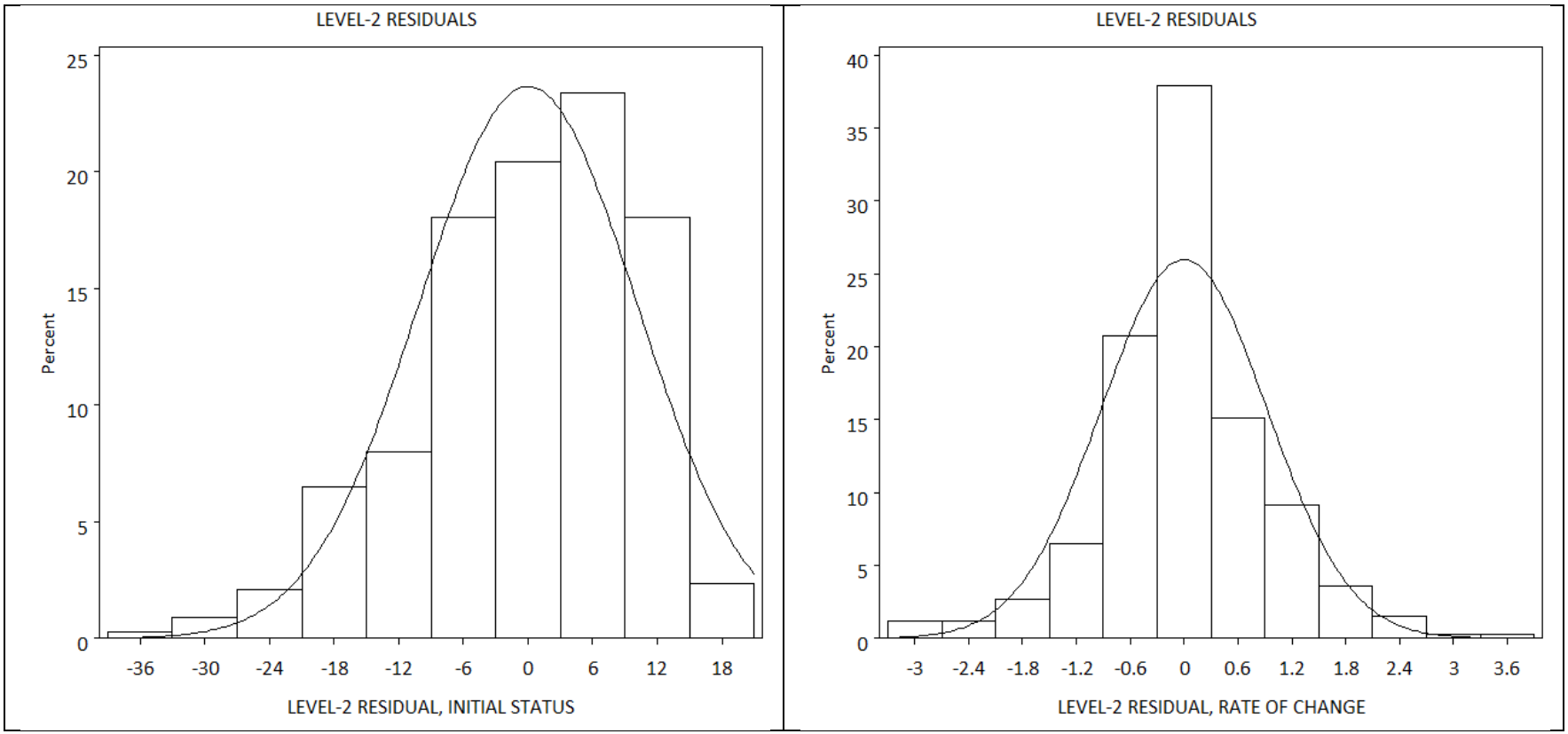

Figure H.6. Histogram of Level 2 Residuals (left, intercept; right, slope). As a complement to Figure H.4, level 2 residuals for the intercept and slope appeared normally distributed.

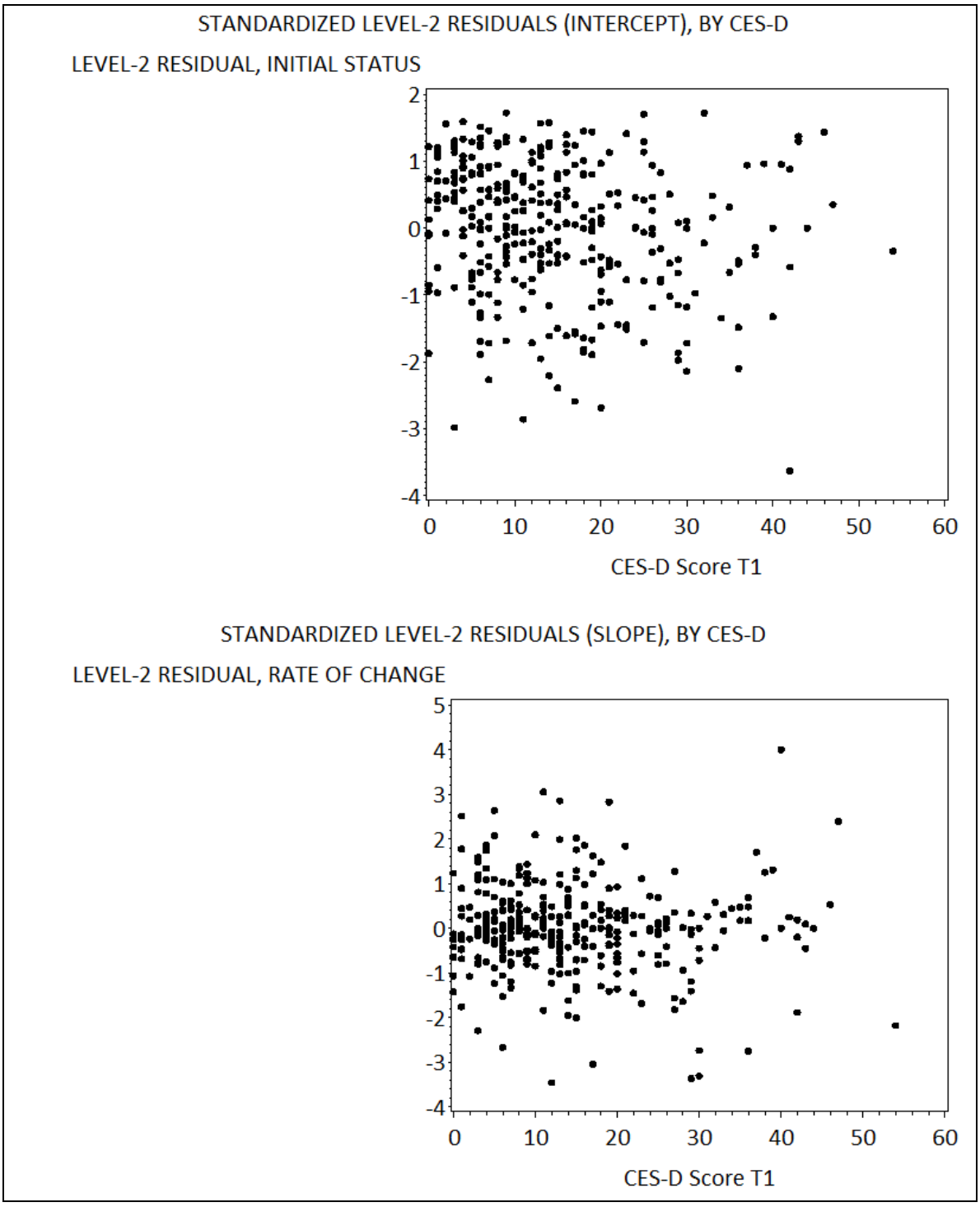

Figure H.7. Standardized Level 2 Residuals Plotted against Maternal CES-D Score (top, intercept; bottom, slope). These plots provide further evidence for assuming normality in the data at level 2 since approximately 95% of the data lie within ±2 standard deviations from the center. CES-D, Center for Epidemiological Studies Depression Scale.

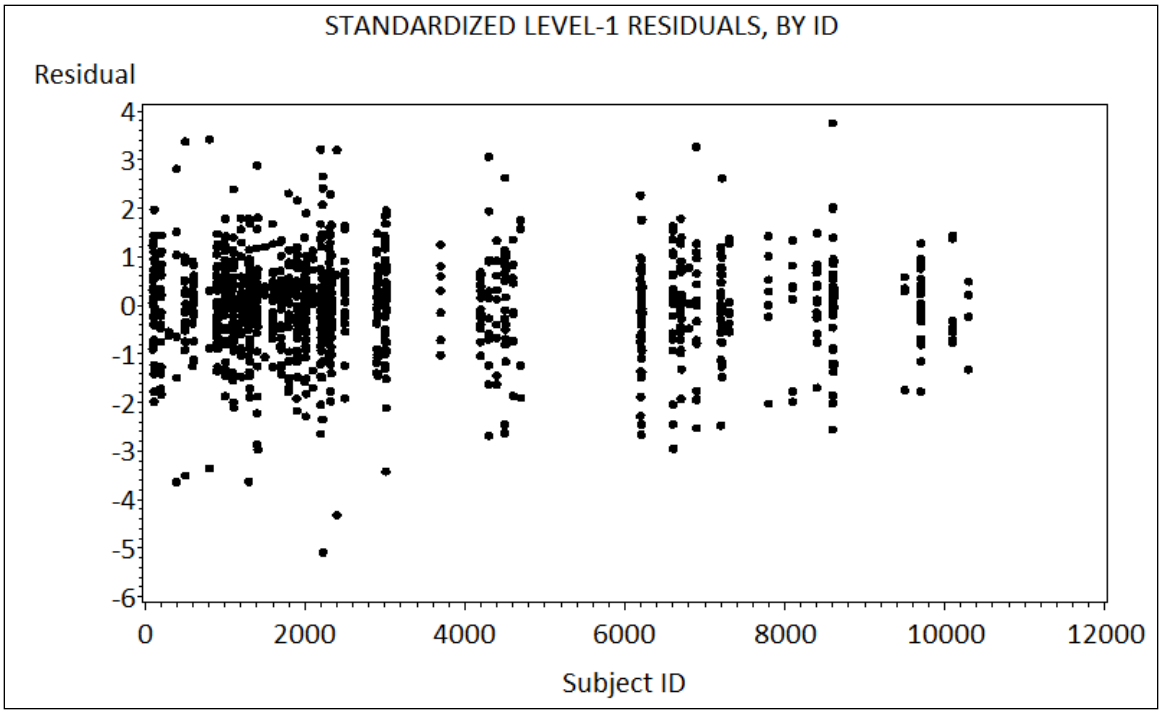

Figure H.8. Standardized Level 1 Residuals Plotted against Subject ID. There appeared to be no extreme individuals in the data at level 1, supporting normal theory.

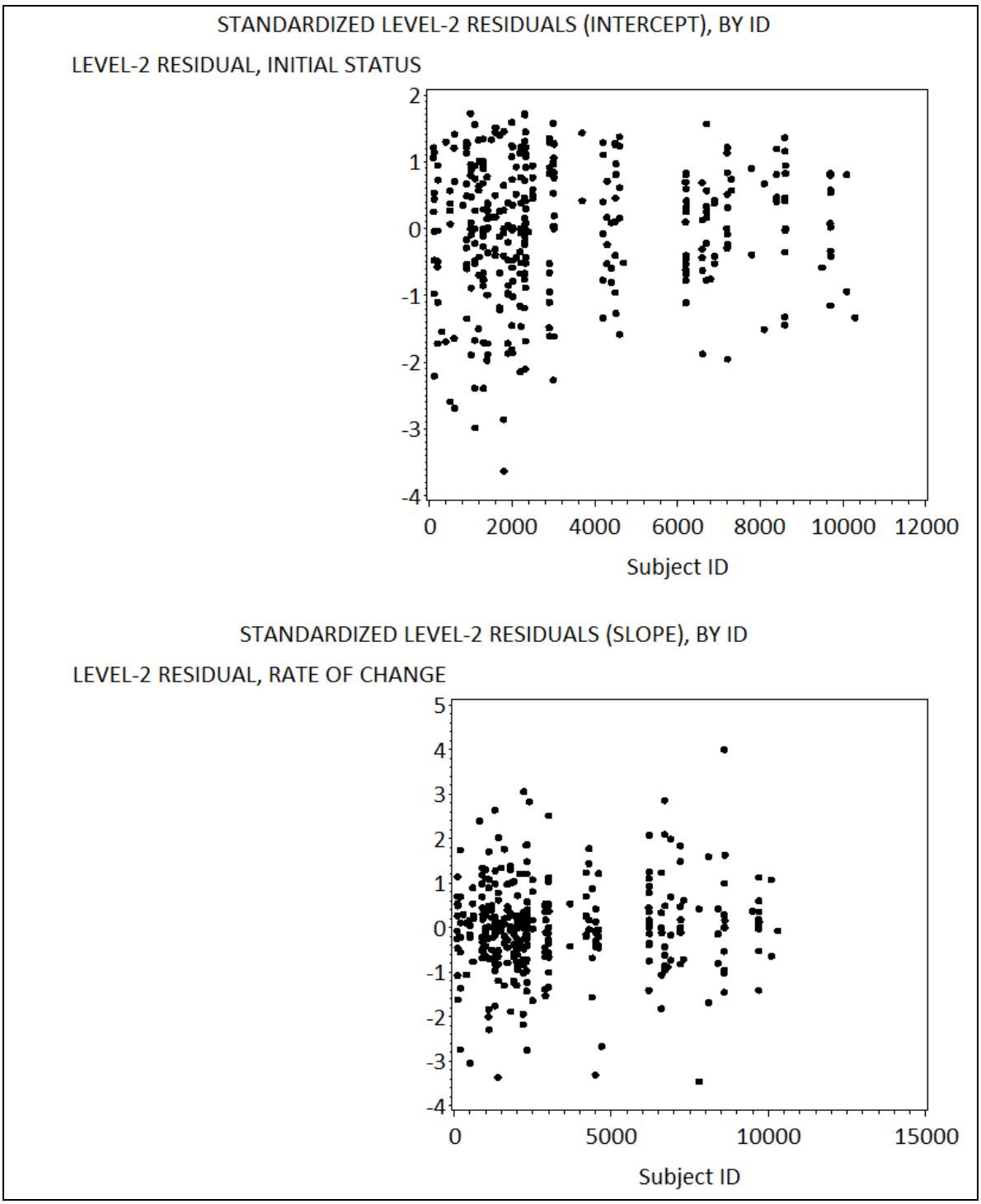

Figure H.9. Standardized Level 2 Residuals Plotted against Subject ID (top, intercept; bottom, slope). There appeared to be no extreme individuals in the data at level 2, supporting normal theory.

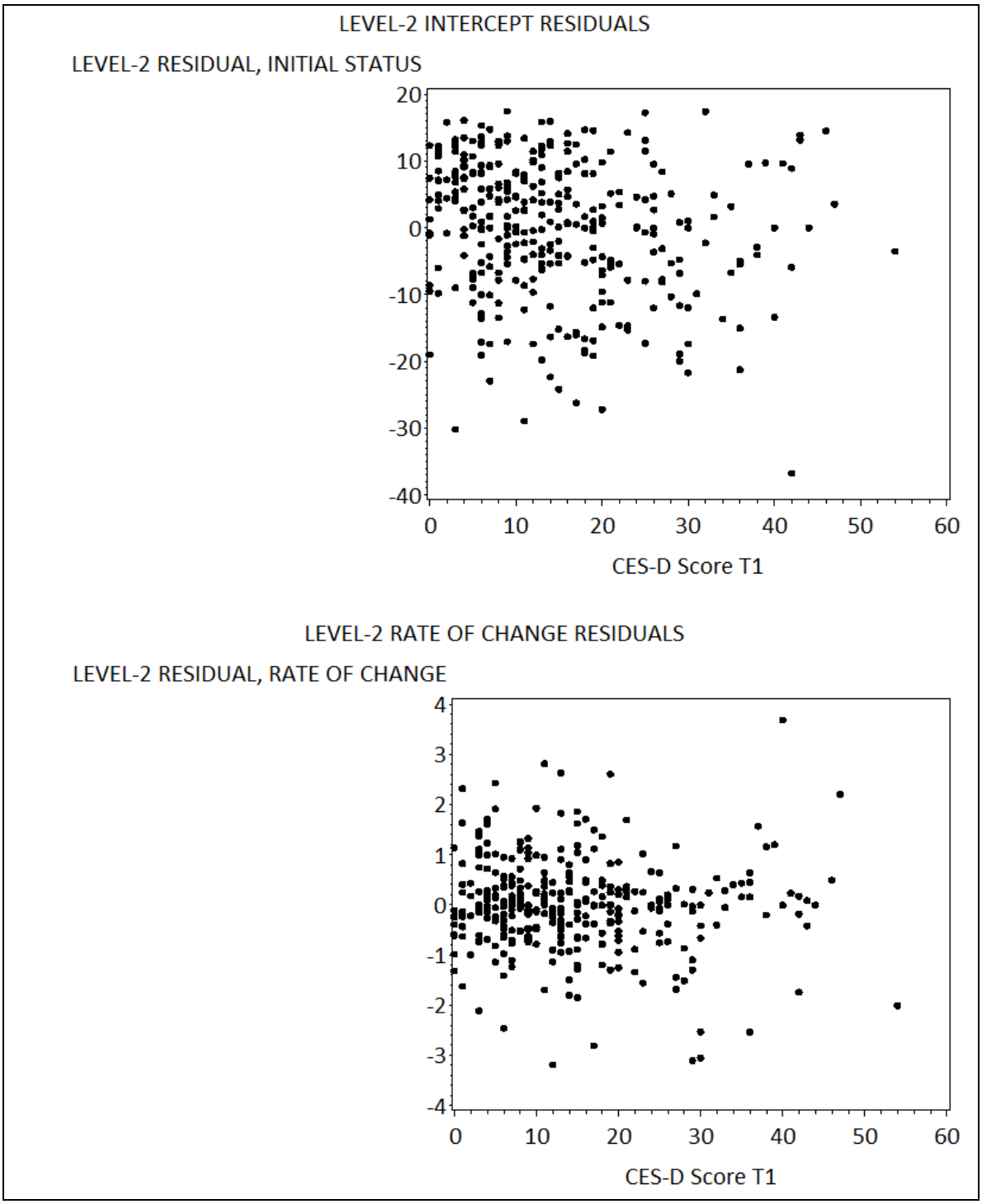

Figure H.10. Examination of the Level 2 Homoscedasticity Assumption (top, intercept; bottom, slope). Plots of the raw residuals of level 2 growth parameters showed that the homoskedasticity assumption was not violated. Residual variances were similar across all values of the Center for Epidemiological Studies Depression Scale (CES-D).

Appendix I

Identification and Treatment of Outliers

Introduction

Outliers were examined prior to conducting all growth curve models. An outlier is any rare or unusual observation that appears at one extreme of the data range.[1] They are important to the extent that they influence the size and precision of estimated β-coefficients. The covariance ratio (COVRATIO) and MDFITS statistics were used to evaluate whether outliers were influential.

Identification of Outliers

The $COVRATIO_i$ statistic measures the role of the ith subject on the precision of estimation.[2] Subjects with a COVRATIO >1 improves precision, whereas subjects with a COVRATIO <1 will improve precision if removed from the model.[2] Subjects were investigated for which:

$$COVRATIO_i > 1 + \frac{[3 \times (1 + k)]}{n}$$

where, k is the number of regression coefficients; and,
n is the number of subjects

$$COVRATIO_i < 1 - \frac{[3 \times (1 + k)]}{n}$$

For this study, COVRATIO statistics that fell outside the range of 0.95 and 1.05 were investigated as potentially influential. As shown in Table I.1, seven subjects in the study sample had COVRATIO values that were outside the range. For brevity, only those subjects that were potentially influential were included in the table. Subjects 511, 1102, 1303, and 6213 had COVRATIO values that were borderline outside the range, whereas subjects 2227, 2404, and 8602 had values that were well outside the

range. These results are illustrated in Figure I.1, which plots COVRATIO statistics against subject ID.

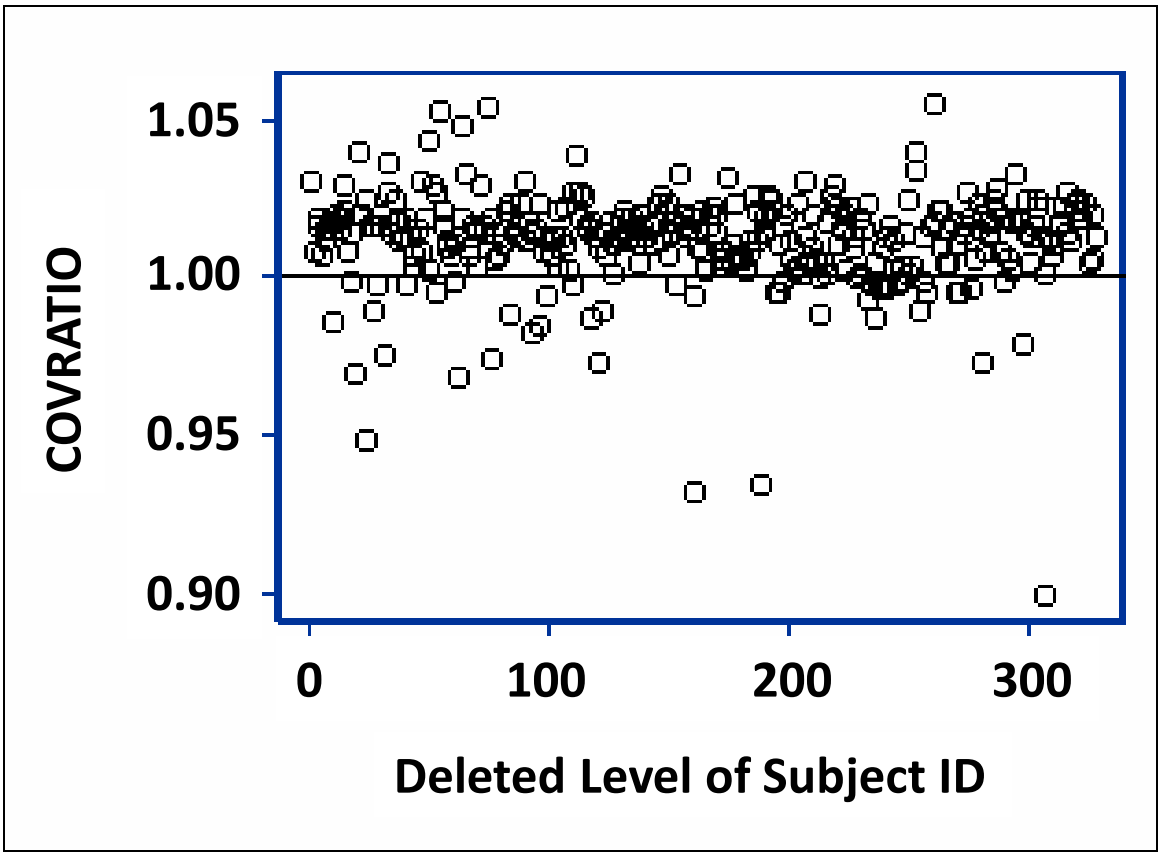

Figure I.1. Plot of COVRATIO Statistics against Subject ID. The plot shows seven potential outliers that may also be influential in the data.

The $MDFITS_i$ statistic is the multivariate $DFITS_i$ statistic that measures the difference between predicted values estimated using all subjects and predicted values obtained by the refitted model omitting the *i*th subject.[2] Large (absolute) MDFITS statistics indicate potentially influential subjects. Subjects were investigated for which:

$$\left|MDFITS_i\right| > 2\sqrt{\frac{(1+k)}{n}}$$

where, k is the number of regression coefficients; and,
n is the number of subjects

For this study, MDFITS >0.25 were investigated as potentially influential. No subjects in the study sample were observed to have a MDFITS value indicative of being influential.

Plots of standardized residuals by individuals were also used to identify outliers in the data. As described in Appendix H, no outliers were observed at level 1 and level 2 using this approach.

Treatment of Outliers

Diagnostics were intended to identify subjects deserving of more careful scrutiny. Raw data for each of the seven subjects identified (using COVRATIO and MDFITS statistics) were reviewed and none of the variables associated with each subject was outside of the realm of possibility. Growth models that sequentially deleted of each of the identified subjects were conducted and results of the reduced model were compared to the full model.[2] There were no significant differences between the seven reduced models and the full model (data not shown). A final reduced model that removed all seven of the identified subjects was then specified and compared to the full model.[2] Again, there were no significant differences between the reduced and full models.

Comparing results from the original and outlier analysis, Table I.2 shows that the proportion of individuals in each trajectory group was similar to the original analysis [group 1 (*low stable*): 59.3% vs. 59.9%; group 2 (*borderline*): 25.1% for both; group 3 (*moderate increasing*): 8.6% vs. 9.1%; and, group 4 (*high decreasing*): 7.1% vs. 5.8%]. Also, the parameter estimates and associated standard errors were nearly identical. As a result, the trajectories illustrated in Figure I.2 remain unchanged from the original analysis.

Similarly, in the analysis examining the impact of maternal depressive symptoms on child health-related quality of life, the parameter estimates and standard errors for

the growth models' fixed effects and variance components were very similar (Table I.3). Trajectories of child health-related quality of life did not significantly deviate from the original model (Figure I.3). The models with potential outliers removed did exhibit better goodness-of-fit based on the deviance statistic; however, this is inadequate to suggest that these individuals be removed from all analyses. Thus, it was concluded that none of the identified subjects was influential and were thus retained in all analyses.

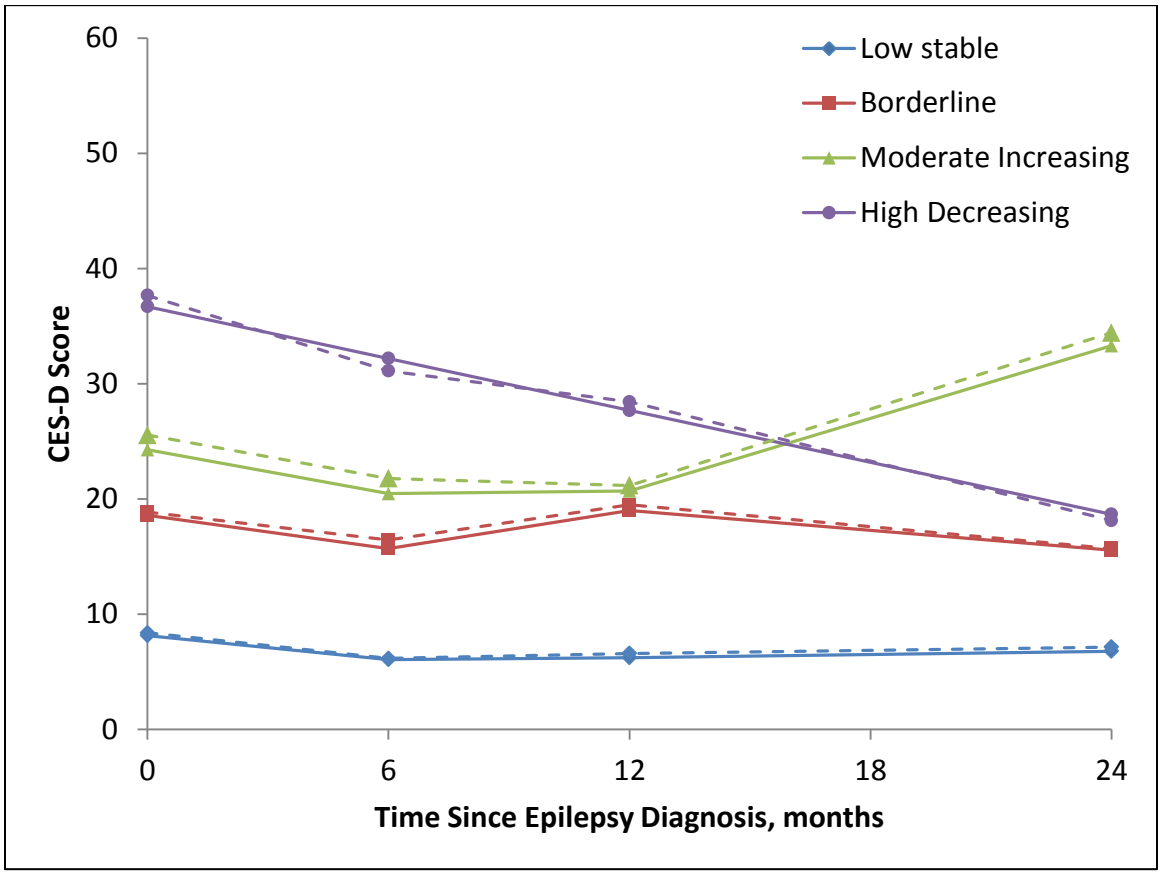

Figure I.2. Trajectories of Maternal Depressive Symptoms during the First 24 Months after having a Child Diagnosed with Epilepsy with Potential Influential Subjects Removed. Solid lines depict observed trajectories (mean CES-D score) and dashed lines predicted trajectories. CES-D, Center for Epidemiological Studies Depression Scale.

It is important to note that this outlier and influence analysis was performed under the assumption that the chosen model is correct. Changing the model structure can alter the conclusions. For example, modeling these data with a fixed slope for each

individual or using an autoregressive covariance matrix may affect the conclusions about which individuals are influential on the analysis and how this influence manifests itself.

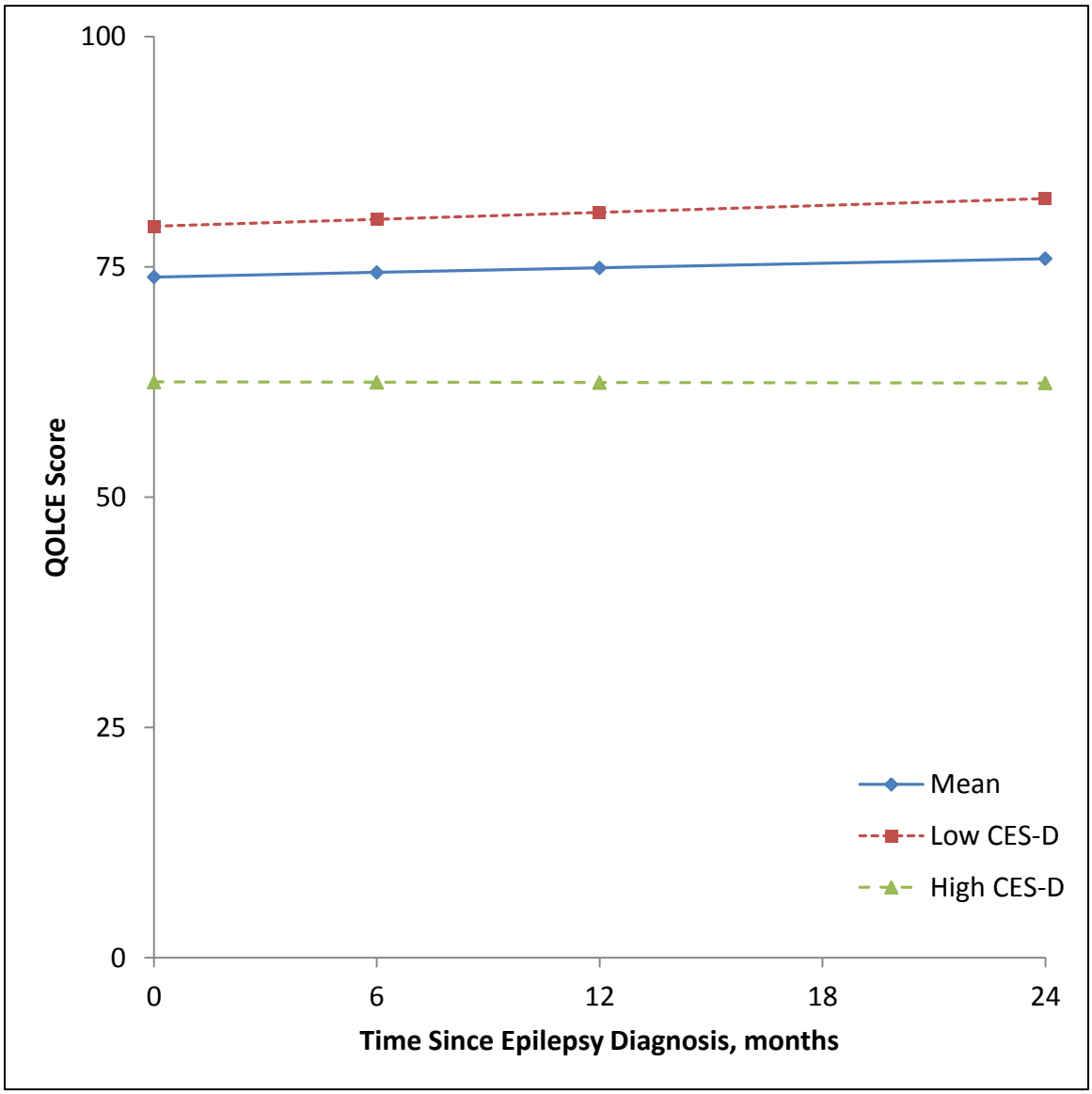

Figure I.3. Change in Child Health-related Quality of Life over 24 Months with Potential Influential Subjects Removed. Child health-related quality of life was measured using the QOLCE. The solid line represents the trajectory for children of average mothers; the dotted line represents the trajectory for children of mothers with a CES-D score in the bottom 5%; and, the dashed line represents the trajectory for children of mothers with a CES-D score in the top 5%. CES-D, Center for Epidemiological Studies Depression Scale; QOLCE, Quality of Life in Childhood Epilepsy.

References

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Table I.1. Influence Diagnostics for Levels of Subject ID.

	Influence Statistics	
Subject ID	**COVRATIO**	**MDFFITS**
511	0.9489	0.01747
1102	1.0527	0.01685
1303	1.0540	0.00872
2227	0.9325	0.02431
2404	0.9354	0.02393
6213	1.0555	0.03087
8602	0.8995	0.05496

Table I.2. Parameter Estimates for the Four-group Trajectory Model of Depressive Symptoms in Mothers of Children with Epilepsy during the First 24 Months after Diagnosis with Potential Influential Subjects Removed.

Group	% Sample	Parameter	Estimate	Standard Error	*t*	*P*-value
1	59.9	Intercept	14.0	1.8	7.9	<0.0001
		Linear	-8.4	2.5	-3.3	0.0008
		Quadratic	2.8	1.0	2.8	0.0058
		Cubic	-0.3	0.1	-2.4	0.0165
2	25.1	Intercept	34.9	3.4	10.4	<0.0001
		Linear	-25.3	4.6	-5.5	<0.0001
		Quadratic	10.2	1.9	5.5	<0.0001
		Cubic	-1.2	0.2	-5.6	<0.0001
3	9.1	Intercept	30.7	1.8	16.6	<0.0001
		Linear	-8.9	1.5	-6.0	<0.0001
		Quadratic	1.9	0.2	7.6	<0.0001
4	5.8	Intercept	41.1	1.3	31.0	<0.0001
		Linear	-4.3	0.4	-11.4	<0.0001

Group 1 represents mothers with *low stable* depressive symptoms, Group 2 *borderline* symptoms, Group 3 *moderate increasing* symptoms, and Group 4 *high decreasing* symptoms.

Table I.3. Growth Models for the Impact of Maternal Depressive Symptoms on Child Health-related Quality of Life with Potential Influential Subjects Removed.

	Model A	Model B	Model C
Fixed Effects			
Final Status			
Intercept	73.28 (0.68)*	75.87 (0.85)*	75.98 (0.72)*
CES-D			-0.44 (0.05)*
Rate of Change			
Time		1.03 (0.18)*	0.95 (0.15)*
CES-D × Time			-0.04 (0.02)†
Variance Components			
Level 1			
Intra-individual	50.52 (2.60)*	38.36 (2.43)*	42.54 (2.37)*
Level 2			
Final Status	130.03 (11.72)*	171.69 (18.13)*	103.70 (9.90)*
Rate of Change		3.41 (0.78)*	0.04 (0.02)†
Covariance		12.32 (3.04)*	0.17 (0.38)‡
Goodness-of-Fit			
Deviance	8028.2	7950.3	7744.7

Values denote β-coefficient (standard error). Model A is the unconditional means model; Model B is the unconditional growth model; Model C is the growth model conditional on maternal depressive symptoms.

*$p<0.0001$, †$p<0.05$, ‡not significant

Appendix J

Examination of Confounding Variables

Examination of potential confounding variables in the moderation and mediation analyses in the impact of maternal depressive symptoms on child health-related quality of life followed the suggestion of Rothman and Greenland.[1] To obtain unbiased estimates of effect, potential confounders were tested *a priori* to the growth curve modeling. Potential confounders tested were maternal age, marital status, employment status, education, parity, child age, child sex, seizure type, age of onset, total number of anti-epileptic drugs, illness severity, behaviour problems, cognitive disability, motor dysfunction, and family income.

Confounding was determined by adding the variable to the model to examine the change in the effect estimate. For the purposes of this study, a collapsibility criterion was used to operationally define confounders as those variables, when entered in the model that resulted in a ≥10% change in the effect estimate of maternal depressive symptoms on child health-related quality of life and would then be retained in the model:[1]

$$\frac{\beta_{unadjusted} - \beta_{adjusted}}{\beta_{adjusted}} \times 100\%$$

Changes in β–coefficients in the presence of confounding variables are presented in Table J.1. Potential confounding variables were tested in each growth curve model used in the moderation and mediation analyses. Results suggested that no variable examined met the collapsibility criterion for definition as a confounding factor. Thus all analyses investigating the impact of maternal depressive symptoms on child health-related quality of life conducted did not control for any other maternal, child, or family characteristic.

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Table J.1. Change in β-coefficients in the Presence of Potential Confounding Variables for Moderation and Meditation Analyses**.**

	CES-D[1]	**CES-D[2]**	**FILE[3]**	**CES-D[4]**	**Family APGAR[5]**
Unadjusted	*-0.4654*	*0.2703*	*-0.6897*	*-0.1143*	*0.8748*
Maternal Age, years	-0.4591 (1.4)	0.2738 (1.3)	-0.6830 (1.0)	-0.1162 (1.7)	0.8721 (0.3)
Marital Status	-0.4556 (2.1)	0.2689 (0.5)	-0.6606 (4.2)	-0.1128 (1.3)	0.8485 (3.0)
Employment Status	-0.4514 (3.0)	0.2695 (0.3)	-0.6758 (2.0)	-0.1125 (1.6)	0.8803 (0.6)
Education	-0.4637 (0.4)	0.2707 (0.1)	-0.6811 (1.2)	-0.1122 (1.8)	0.8959 (2.4)
Parity	-0.4709 (1.2)	0.2703 (0.1)	-0.6966 (1.0)	-0.1145 (0.2)	0.8707 (0.5)
Child Age, years	-0.4653 (0.1)	0.2698 (0.2)	-0.6867 (0.4)	-0.1146 (0.3)	0.8639 (1.2)
Child Sex	-0.4678 (0.5)	0.2737 (1.3)	-0.6926 (0.4)	-0.1132 (1.0)	0.8983 (2.7)
Seizure Type	-0.4781 (2.7)	0.2755 (1.9)	-0.6996 (1.4)	-0.1171 (2.4)	0.9314 (6.5)
Onset Age, years	-0.4609 (1.0)	0.2724 (0.8)	-0.6737 (2.3)	-0.1124 (1.7)	0.9030 (3.2)
Total AEDs	-0.4662 (0.2)	0.2764 (2.3)	-0.7127 (3.3)	-0.1220 (6.7)	0.8722 (0.3)
Illness Severity, GASE	-0.4236(9.0)	0.2724 (0.8)	-0.7027 (1.9)	-0.1201 (5.1)	0.8836 (1.0)
Behaviour Problems	-0.4761 (2.3)	0.2724 (0.8)	-0.7400 (7.3)	-0.1203 (5.2)	0.9037 (3.3)
Cognitive Disability	-0.4759 (2.3)	0.2744 (1.5)	-0.7566 (9.7)	-0.1188 (3.9)	0.8754 (0.1)
Motor Dysfunction	-0.4764 (2.4)	0.2797 (3.5)	-0.7450 (8.0)	-0.1182 (3.4)	0.8674 (0.8)
Family Income	-0.4277 (8.8)	0.2517 (7.4)	-0.6463 (6.7)	-0.1111 (2.9)	0.8129 (7.6)

Values denote β (Δ%).

AEDs, anti-epileptic drugs; CES-D, Center for Epidemiological Studies Depression Scale; Family APGAR, Family Adaptability, Partnership, Growth, Affection, Resolve; FILE, Family Inventory of Life Events and Changes; GASE, Global Assessment of Severity of Epilepsy; QOLCE, Quality of Life in Childhood Epilepsy.

[1]QOLCE regressed on CES-D (X→Y)

[2]FILE regressed on CES-D (X→M)

[3]QOLCE regressed on FILE (M→Y)

[4]Family APGAR regressed on CES-D (X→M)

[5]QOLCE regressed on Family APGAR (M→Y)

Curriculum Vitae

Name Mark Anthony Ferro

Education

PhD, Epidemiology and Biostatistics
The University of Western Ontario, 2011

MSc, Community Health and Epidemiology
University of Saskatchewan, 2006

BSc(Hon), Biochemistry and Molecular Biology
McMaster University, 2004

Appointments

Postdoctoral Fellow
Children's Health Research Institute
The University of Western Ontario, 2011

Trainee
Children's Health Research Institute and Lawson Health Research Institute
The University of Western Ontario, 2006-2011

Professional Experience

Consultant
Biostatistical Support Unit
Department of Epidemiology and Biostatistics
The University of Western Ontario, 2011

Statistical Consultant
LivDerma Inc., 2010-Present

Graduate Teaching Assistant
Department of Epidemiology and Biostatistics
The University of Western Ontario, 2008-2010

Research Assistant
Saskatchewan Cancer Control Research Program
University of Saskatchewan, 2005-2006

Associate Product Manager
Inflammation Business Unit
Amgen Canada Inc., 2003

Medical Research Associate
Inflammation Business Unit
Amgen Canada Inc., 2002

Tutor
Hamilton Catholic District School Board, 2001

Scholarships

Fredrick Banting and Charles Best Canada Graduate Scholarship Doctoral Award
Canadian Institutes of Health Research, 2008-2011

Schulich Scholarship for Graduate Research
The University of Western Ontario, 2007-2010

Western Graduate Research Scholarship
The University of Western Ontario, 2007-2010

Student Bursary
McLaughlin Centre for Population Health Risk Assessment
University of Ottawa, 2009

Ontario Graduate Scholarship
Ministry of Training, Colleges and Universities, 2008-2009 (declined)

Ontario Graduate Scholarship
Ministry of Training, Colleges and Universities, 2007-2008

Graduate Scholarship
Department of Paediatrics
The University of Western Ontario, 2006-2007

Graduate Scholarship
College of Medicine
University of Saskatchewan, 2005

Honours and Awards

Top 10% Research Award
American Epilepsy Society, 2010

Trainee Travel Grant
Children's Health Research Institute
The University of Western Ontario, 2007, 2009, 2010

Clinical Award (Oral Presentation)
Paediatrics Research Day
The University of Western Ontario, 2010

Top Presenter
Aging/Health Event
Department of Sociology
The University of Western Ontario, 2010

Travel Award
Margaret Moffat Research Day
The University of Western Ontario, 2010

Young Investigator Award
American Epilepsy Society, 2009

Clinical Award (Poster Presentation)
Paediatrics Research Day
The University of Western Ontario, 2009

Presenter Award
Eastern Canada Health Outcomes Meeting, 2009

Travel Award
Eastern Canada Health Outcomes Meeting, 2009

Travel Award
Institute of Human Development, Child and Youth Health
Canadian Institutes of Health Research, 2009

Travel Award, Society of Graduate Students
The University of Western Ontario, 2008

President/Student Fund Grant
University of Saskatchewan, 2005

Essay Award
Canadian Interdisciplinary Network for Complementary and Alternative Medicine Research, 2005

Graduate Scholarship
Cancer and Complementary and Alternative Medicine Research, 2005

Dean's Honour List, McMaster University, 1999-2004

Research Grants

Speechley KN, Camfield CS, Ferro MA, Levin SD, Smith ML, Wiebe S, Zou GY. *Health-related quality of life in children with epilepsy: a long-term follow-up*. Canadian Institutes of Health Research: $709,307 (requested). Co-investigator, 2011

Ferro MA. *Depressive symptoms in mothers of children with new-onset epilepsy: a prospective study.* Graduate Thesis Research Award, The University of Western Ontario: $1,500. Principal Investigator, 2008

Ferro MA, Speechley KN. *Complementary and alternative medicine use in children with juvenile idiopathic arthritis.* Graduate Studentship Grant, Canadian Interdisciplinary Network for Complementary and Alternative Medicine Research: $5,000. Principal Investigator, 2007

Ferro MA, Leis A. *Prevalence of traditional Chinese medicine use among Chinese cancer patients in British Columbia, Canada.* Graduate Studentship Grant, Canadian Interdisciplinary Network for Complementary and Alternative Medicine Research: $5,000. Principal Investigator, 2005

Research Projects

VanHouwelingen L, Ferro M, Colquhoun P. *Natural Orifice Translumenal Endoscopic Surgery (NOTES): a Canadian patient perspective*, 2009-Present

Speechley KN, Smith ML, Camfield CS, Wiebe S, Zou GY, Levin SD, Ferro MA. *Health-related quality of life in children with epilepsy: the first two years after diagnosis in parents' eyes,* 2003-2011

Publications

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Invited Lectures

"Depressive symptoms in mothers of children with new-onset epilepsy: a prospective study." School of Graduate and Postdoctoral Studies, The University of Western Ontario, London, Canada, April 19, 2011

"Depression in mothers of children with epilepsy." Purple Day Conference, Epilepsy and Seizure Disorder Resource Center, Kingston, Canada, March 26, 2011

"How to be a successful graduate student." Department of Epidemiology and Biostatistics, The University of Western Ontario, London, Canada, September 8, 2010

"Conducting a health survey research study." Department of Epidemiology and Biostatistics, The University of Western Ontario, London, Canada, February 20, 2008

"Complementary and alternative medicine (CAM) use in children with juvenile idiopathic arthritis (JIA): prevalence and associated outcomes." Division of Rheumatology, Hospital for Sick Children, Toronto, Canada, August 21, 2007

"Use of traditional Chinese medicine and other complementary and alternative medicine among Chinese cancer patients in British Columbia." Palliative Care and Cross-cultural Research Day, Vancouver, Canada, June 6, 2006

"What to expect at university." St. Jean de Brebeuf Catholic Secondary School, Hamilton, Canada, May 31, 2002

Media Releases

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Wendling P. "Depression common in mothers of epileptic children." Internal Medicine News, Chicago, United States, September 21, 2010, URL: http://www.internalmedicinenews.com

Extracurricular Service

Children's Health Research Institute "Rising Researcher"
Canadian Council of Child Health Research Symposium
Canadian Association of Paediatric Health Centres Conference, 2010

Expert Consultant
'Ask the Experts' Session for Scholarship Applicants
School of Graduate and Postdoctoral Studies
The University of Western Ontario, 2010

Ad Hoc Reviewer
Psychiatric Research, Public Health, 2009-Present

Decanal Selection Committee
Associate Dean
Graduate and Postdoctoral Studies for the Schulich School of Medicine and Dentistry
The University of Western Ontario, 2009

External Reviewer
SickKids Foundation
Complementary and Alternative Health Care Research Grants Program, 2009

Student Representative
Epidemiology and Biostatistics
The University of Western Ontario, 2008-2009

Representative
Society of Graduate Students
The University of Western Ontario, 2007-2008

Graduate Student Representative
University of Saskatchewan, 2004-2005

Secretary
Biology Society
McMaster University, 2001-2002

VP Communications
Biology Society
McMaster University, 2000-2001

Professional Affiliations

International Society for Quality of Life Research (ISOQOL), 2009-2010

Society for Epidemiologic Research (SER), 2008-Present

Canadian Society for Epidemiology and Biostatistics (CSEB), 2008-Present

Canadian League Against Epilepsy (CLAE), 2008-Present

Canadian Epilepsy Research Initiative (CERI), 2008-Present

American Association for the Advancement of Science (AAAS), 2007-Present

Canadian Pediatric Complementary and Alternative Medicine Network (PedCAM), 2006-Present

Canadian Interdisciplinary Network for Complementary and Alternative Medicine Research (IN-CAM), 2004-Present