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Exploring the Relationship Between Early Severity of Epilepsy and Depressive Symptoms in Youth Ten Years after Diagnosis

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Abstract

This study assessed the association between early severity of epilepsy and subsequent depressive symptoms in youth and the extent to which family and clinical factors mediated this relationship. Data were obtained from the Health-Related Quality of Life in Children with Epilepsy Study, a multi-centre prospective study of children with new-onset epilepsy. A multiple linear regression analysis revealed severity of epilepsy 2 years post-diagnosis to be positively associated with depressive symptoms 10 years post-diagnosis (b=2.10, 95%CI:0.42,3.79). The results of generalized estimating equation models found family functioning, family resources, parental depressive symptoms, and antiepileptic drug use to not be mediators. Five-year seizure freedom mediated this relationship (ab=1.22, 95%CI:0.35,2.09), decreasing the magnitude of the total effect of severity of epilepsy on depressive symptoms by 58%. These findings provide insight on long-term effects of the early clinical presentation of epilepsy. Clinical efforts to achieve remission may be targeted to reduce risk of depressive symptoms.

Keywords: Childhood epilepsy, Depressive symptoms, Adolescents, Young adults, Family environment, Longitudinal study

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List of Abbreviations

ILAE	International League Against Epilepsy
AED	Antiepileptic Drug
PWE	People with Epilepsy
HRQoL	Health-Related Quality of Life
HADS	Hospital Anxiety and Depression Scale
CDI	Children's Depression Inventory
GASE	Global Assessment of Severity of Epilepsy
CES-D	Center for Epidemiological Studies Depression Scale
Family APGAR	Family Adaptability, Partnership, Growth, Affection and Resolve
FIRM	Family Inventory of Resources for Management
GEE	Generalized Estimating Equation
FCC	Family-Centered Care

Chapter 1

1 Introduction

This thesis examines the relationship between overall early severity of epilepsy during childhood as a predictor of subsequent depressive symptoms during adolescence and early adulthood. Moreover, it explores whether aspects of the family environment and proximal clinical factors play a part in the pathway of this relationship. Clarifying the role of familial and clinical factors on the risk of depressive symptomology will inform researchers and clinicians of potential targets to implement interventions. This may ultimately provide an opportunity to lower the risk of depression by targeting family factors of youth who may have had severe epilepsy during their childhood.

This chapter will provide background information regarding epilepsy and introduce the burden of depression in youth who are living with epilepsy.

1.1 Background

1.1.1 Epilepsy Overview

Epilepsy is a neurological condition characterized by a predisposition to recurrent epileptic seizures (1). To be diagnosed with epilepsy, a person must fit at least one of the following criteria: 1) two or more unprovoked seizures occurring 24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general reoccurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or 3) diagnosis of an epilepsy syndrome (1). The International League Against Epilepsy's (ILAE) classification includes three major categories of seizures: focal (motor or non-motor), generalized (motor or absence), or unknown onset (motor or non-motor) (1). Seizure type is based on the origin of seizures in the brain and are useful for communication purposes in clinical care and research (2,3). Generalized seizures originate from large areas of the cortex in both hemispheres, whereby focal seizures, formally referred to as partial seizures, arise from small loci of the cortex in only one hemisphere and may originate in subcortical structures (2). There is almost always a loss of consciousness associated with generalized seizures; however, in the case of focal seizures, impaired awareness may or may not occur (2). It is possible for patients to

outgrow their epilepsy, especially for those with childhood-onset mesial temporal lobe epilepsy who had their hippocampal sclerosis resected (1). For epilepsy to be considered resolved, a person must be seizure-free for at least a decade and not have taken antiepileptic drugs (AED) for the past five years or be past the applicable age for their age-dependent epilepsy (1). There is no formal definition for epilepsy being in remission, however experts have proposed that five years of seizure freedom and two years off seizure medication be used due to the modest differences in relapse rates between these time points and that of the criteria for epilepsy being resolved (4).

The primary medical treatment received by the majority of people who have epilepsy is drug therapy in the form of antiepileptic drugs. AEDs provide good seizure control for 65% of patients with new-onset epilepsy (5). Over a year, AEDs completely eliminate seizures in 50% of new-onset patients, and reduce the frequency of seizures in 17% of people, leaving nearly 33% of AED users with uncontrolled seizures (5). Approximately 30% to 40% of patients do not achieve full control over their seizures with a single AED, and their neurologists must experiment with different AEDs or combinations of AEDS to gain seizure control (5–7). Some patients experience drug-resistant epilepsy and may be candidates for surgery. Resective surgery involves removal of the localized epileptogenic tissue, and has been found to control seizures in 64% to 70% of drug-resistant temporal lobe epilepsy patients alongside AED treatment (5,8). Prior to attempting surgery or when surgery fails, vagus nerve stimulation is a non-invasive palliative treatment option that has been proven to be effective for people who have refractory focal onset-epilepsy (9).

1.1.2 Childhood-Onset Epilepsy

There are many possible causes of childhood-onset epilepsy. It may have a genetic or molecular basis, occur post-infection or following an acute brain injury, or be due to abnormalities of cortical development, neurocutaneous disorder or hippocampal sclerosis (10). Although the majority of children reach remission, 13% to 17% of patients have refractory (intractable) epilepsy which is often associated with a poor prognosis (10). A large portion of patients (30%) have pharmacosensitive epilepsy for which they achieve good seizure control and may have a spontaneous remission after a few years.

Pharmacodependent epilepsy requires individuals (20%) to take their medication but they do not achieve remission. Lastly, people with benign epilepsies may never require treatment and achieve remission after a few years (10).

Over three quarters of children with idiopathathic (no apparent cause) epilepsy, the most common form, are expected to be in remission by two years following diagnosis (11). Children who continue to have frequent seizures during the first year of treatment are at an increased risk of developing intractable epilepsy and never achieving one-year terminal remission (12). Seizure frequency is negatively correlated with epilepsy outcomes because it is ultimately reflective of severity of epilepsy (13).

1.1.3 Prevalence of Epilepsy

Globally, 10.5 million children up to the age of 14 are living with epilepsy, which constitutes 25% of all cases (14). The prevalence of childhood epilepsy ranges from 3 to 7 per 1000 people in developed countries, as compared to 9 to 22 per 1000 people in developing countries (15). The higher prevalence of epilepsy in developing countries may be attributed to parasitic infections, a common cause of epilepsy in these countries (15). The incidence of epilepsy in Nova Scotia, Canada was found to decrease with age, at 118 per 100,000 children under the age of 1, 48 per 100,000 for children between the ages of 1 to 5 years, 43 per 100,000 for children aged 6 to 10 years, and 21 per 100,000 for children aged 11 to 15 (16). For children and youth up to the age of 19, the prevalence of epilepsy has been estimated to be 4.7 per 1000 people in Manitoba, Canada, with the highest prevalence in those aged 15 to 19 years (7.19 per 1000 people) and the lowest among children under the age of 9 (17). From two Canadian population based studies, the prevalence of epilepsy among adolescents aged 12 to 14 years was estimated to be 2.9 to 4.4 per 1000 people, and for youth aged 15 to 24 years, 4.8 to 3.6 per 1000 people (18).

The estimated median number of people with lifetime epilepsy in developed countries is 6.8 million of which 84% are active cases (19). In developing countries it is much higher at 45 million for rural areas and 17 million for urban areas of which, respectively, 38% and 59% are active cases (19). For people of all ages, the prevalence of self-reported epilepsy in Ontario has been estimated to be 5.8 per 1000 people (20). Also in Ontario between the years of 2004/05 and 2010/11, the prevalence of epilepsy has

increased from 63,898 cases to 89,867 cases (21). Among adults, the prevalence estimates for active epilepsy in Canada range from 5 to 10 per 1000 people (22). Reports from two Canadian population surveys indicate a significantly higher prevalence of people with self-reported epilepsy among those who have a low educational attainment and income and those who are unemployed (18). This is consistent with a recent study in the United Kingdom where epilepsy was more common in the those who had less education, lower income, and were less satisfied with their employment (23).

1.2 Depression in Adolescents and Young Adults with Epilepsy

Adolescence may be a difficult stage in life due to the rapid physical, social, and psychological development that occurs during this period (24). For youth with epilepsy, it may be more challenging as they try to gain independence from their parents and transition into being responsible for the management of their medical condition. Additionally, these youth continue to cope with epilepsy-related stigma and limitations that the disease may have placed affecting their social and physical functioning (24,25). The occurrence of puberty during early adolescence is a time where the frequency of seizures may be altered, depending on seizure type, thereby potentially changing the severity of their epilepsy (26). Some concerns expressed by adolescents living with epilepsy have been related to education/career options, potential effects of discontinuing AEDs, being eligible to drive, and leisure activities and alcohol use (27). A third of children and teenagers with epilepsy expect the disease to hinder their lives in the future, with the most commonly perceived problems being regarding employment opportunities (73%), travelling and exploring (37%), and education (36%) (28). Among teenagers without epilepsy, a 2001 survey of high school students found that half were not sure if people with epilepsy (PWE) could drive cars, work, or should have children, a third indicated that they would not date a person who has epilepsy, and 63% thought that youth with epilepsy were likely to get bullied (29). Accordingly, along with coping with the daily struggles of growing up with epilepsy and worrying about their future, adolescents may have to deal with being treated differently by their peers.

Depression is a mood disorder that may present with a loss of energy, feelings of guilt, difficulty concentrating, hopelessness, or thoughts of suicide (30). The incidence of

depression in adolescents tends to increase with age, peaking in late adolescence/early adulthood (31,32). As adolescents mature into young adults there may be new pressures with becoming of legal age for alcohol and tobacco use, achieving higher levels of education, beginning occupations, or even marriage. Thus, it is not surprising that adolescents and young adults tend to have a higher prevalence of depression as compared with children (33). A study examining the temporality of mental health disorders in the United States found that 75% of adults with a mental health disorder had an age of onset before 24 years (34). In the year 2011, an estimated one million Canadian youth were living with a mental illness, and this is expected to increase to 1.2 million by the year 2041 (35).

Depression may be more problematic for youth with chronic health diseases such as epilepsy due to the added stress of the disease with regular life stage stressors. Unfortunately, many cases of mild and moderate depression among PWE go unrecognized and under-diagnosed by physicians due to the depressive and anxiety symptoms being assumed to be a reflection of the normal adaptation process to epilepsy (36). Symptoms of depression including decreased concentration, fatigue, and sleep disturbances are also mutual side effects of AEDs (37). Therefore, it is essential to closely monitor the mental health of youth with epilepsy. Factors predictive of psychopathology in PWE are multifactorial [epilepsy disease and treatment-related, psychosocial (including familial factors), and demographic] (38). The possible causes of depression include: the endocrine and/or metabolic effects of seizures, common pathogenic mechanisms between the two conditions, adverse effects of various AEDs, and or the psychological response to having epilepsy due to its mental, physical and social challenges (39). Depressive symptoms occurring in PWE can be categorized as either ictal (symptoms are a clinical manifestation of a seizure), peri-ictal (symptoms precede and or/occur following the seizure) and interictal (symptoms occur independent of the seizures) (40). Interictal depression is the most common and can present as minor or major depression, dysthymic disorder, or bipolar disorder (40).

1.2.1 Prevalence of Depression in People with Epilepsy

The Canadian Community Health Survey 2000/2001 cycle found the prevalence of

depression to be significantly higher (13%) among people over the age of 12 living with epilepsy as compared to those without epilepsy (7.2%) (41). In Alberta, the prevalence of depression among PWE of all ages was 28.2% based on administrative health data (42). For Canadians over the age of 15 years with epilepsy, the lifetime prevalence of a major depressive disorder was 17.4% in 2002 (43). The U.S. *HealthyStyles* 2004 survey produced results consistent with Canadian studies where adults ever diagnosed with epilepsy were 2.5 times more likely to self-report depression in the previous year as compared to people without epilepsy, after controlling for demographic factors (32.6% vs. 15.5%) (44). Although a larger proportion of people with active epilepsy self-reported depression compared to people with inactive epilepsy (39.7% vs. 23.8%), the difference in the likelihood of having depression between the two groups was not statistically significant (44). This suggests that the current state of epilepsy may not be the only predictor of psychiatric problems in this population, but perhaps common past or current biological or psychosocial mechanisms are also of importance.

1.2.2 Implications of Depression for People Living with Epilepsy

Depression is one of the most prevalent psychiatric illnesses among PWE with the possibility of the relationship being bidirectional (40). A few studies have found people with past depressive disorders to be at an increased risk of developing seizures. However, it may not be the case that depression causes epilepsy but rather there are common pathologic mechanisms responsible for the co-occurrence of these two conditions (40). The primary focus of research in this field is how depressive disorders develop in those diagnosed with epilepsy leading to negative implications on their quality of life.

For the general public in 1998, the economic burden associated with depression and distress in Canada was estimated to be $278 million attributed towards direct costs due to psychologist and social worker visits and $6.02 billion for indirect costs due to missing work (45). Among children and youth, ages 10 to 24 years residing in Ontario, there has been a relative increase of 32.5% in mental health-related emergency department visits, 15.8% in office-based physician visits, and 53.7% in hospitalizations between 2006 and 2011 (46). Moreover, early adolescent depression has been found to increase the risk of having poorer self-perceived general health, increased health care

utilization, and increased work impairment during early adulthood while controlling for concurrent depression (47). Also in Ontario in 2010/11, the average costs of health systems use among prevalent and incident cases of epilepsy were $7283 and $10,631, respectively (21). The majority of these costs were attributed to hospital care, physician, and other health care professional services, and long-term or home care. PWE were also found to be four times more likely to be hospitalized for depression compared to those without epilepsy (48). Thus, untreated depression among PWE is likely to increase the use of healthcare resources with a greater need of resources for individuals with severe symptoms (49).

Early detection and treatment are exceptionally important among PWE due to the risk of untreated depression possibly interfering with condition self-management behaviours, leading to poor health outcomes (50,51). Non-adherence to AEDs is more common among depressed epilepsy patients, and the presence of co-morbid depression has also been found to be associated with a lack of response to AEDs (52–54). The occurrence of major depression may also affect the clinical course of epilepsy, with patients experiencing more difficulty with the cognitive, emotional, and physical aspects of recovering from a seizure (55).

Untreated depression in adolescents is associated with a high risk of self-harm and suicide, with more than half of suicides having a history of depression (56,57). The average incidence of suicide is 10-fold higher among patients with epilepsy as compared to the general public (40,58). In Canada, the lifetime prevalence of suicidal thoughts in PWE is significantly higher compared to people without epilepsy (25% vs. 13.3%) (43). A higher rate of death by suicide is also present among those with epilepsy (5% vs. 1.4%) (59). The high risk of suicide among epilepsy patients may be related to common mechanisms associated with the development of both major depression and epilepsy, as both a history of attempted suicide and major depression have been found to be associated with the development of unprovoked seizures (60).

Untreated depression may also have substantial implications on the health-related quality of life (HRQoL) of people living with epilepsy. HRQoL, a construct referring to the “subjective and objective impact of dysfunction associated with an illness or injury, medical treatment, and health care policy”, is considered the most important health

outcome with respect to chronic health conditions by the ILAE Commission (61,62). Previous research has found patients' HRQoL to be more strongly associated with mood states as compared to severity and frequency of seizures (63,64). Additionally, depressive symptoms have been shown to be associated with poor HRQL regardless of seizure type among adults (55). A strong linear relationship has been found to exist between depressive symptoms and HRQoL, with more symptoms being associated with lower HRQoL scores (64). Among adults, depression accounts for 30% to 35% of the variance is HRQoL, whereby demographic and clinical factors only account for 15% to 20% (64).

Chapter 2

2 Literature Review

This chapter provides an overview of prior literature on the severity of epilepsy as a risk factor for depression and the importance of family environment for patients. Studies were located by searching the following electronic databases: PsychINFO, Pubmed (MEDLINE), and CINAHL. Furthermore, the ancestry method was implemented to identify studies that were not found in the initial searches by locating additional articles through reviewing the reference lists of studies.

The first two sections review literature on the relationship between severity of epilepsy and other clinical factors with depression (Sections 2.1-2.2). Sections 2.3-2.5 review literature on the association between family factors and depression in patients with epilepsy. The final section (Section 2.6) presents an overview of the limitations characterizing the literature to date.

2.1 Severity of Epilepsy

Severity of epilepsy encompasses all aspects of the disease, incorporating both clinical features, such as frequency and severity of seizures, and its level of disruptiveness to the patient's functioning, such as falls or injuries during seizures and side effects or interference of drugs with daily activities (65,66). Difficulty with seizure control is likely to be associated with lifestyle restrictions and negative consequences on patients' mental health (67,68). Thus, physicians aim to manage disease severity over time to reduce the risk of side effects and improve long-term outcomes through the use of treatments and/or by recommending interventions.

2.2 Early Childhood Severity of Epilepsy and Depression

Living with a chronic childhood illness such as epilepsy may have implications on mental health during adulthood. Youth and adults with childhood epilepsy experience more psychiatric disorders, irrespective of seizure mediation use or having gained full seizure control, as compared to the general public (69–71). This is not surprising given that

several childhood chronic conditions have been found to be associated with psychiatric problems and lower quality of life in adulthood (72). With regards to epilepsy, it is unknown whether the disease itself is the root of unfavourable adulthood outcomes, or whether unfavourable outcomes are due to consequences and side effects of illness, such as modifications in the family environment.

The time around the diagnosis of a disease is a difficult period for both the child and family. Over time, once the condition becomes chronic, the long-term impact of the condition is perceived to be greater due to the prolonged stress (73). Following diagnosis, the state of a disease may change for the better, become worse, or remain stable over time. The effect that the disease may have on long-term psychological and physical stress may depend on whether the disease is quickly managed and creates minimal disruptions, as compared to a chronic course of illness with a greater burden (73).

Although epilepsy is a chronic disease, the majority (65%) of children diagnosed gain full control of their seizures using medications within the first two years and may discontinue treatment (74). As a general rule of thumb for children with a promising prognosis, physicians recommend discontinuing AED treatment after one to two years of seizure freedom (74–76). The remaining children who do not gain seizure control within the early years following diagnosis are the ones at risk of having retractable epilepsy (77). Specifically, those whose seizures do not remit within two years of AED use (35%) are unlikely to ever be seizure free for life without an intervention (74). As such, the severity of epilepsy a few years after diagnosis is likely a better predictor of long-term course, as the disease prognosis becomes apparent by this time.

Severity of epilepsy has not yet been tested prospectively as a risk factor for depression, but more severe seizures and epilepsy have been found to be associated with depression, emotional problems, internalizing problems, self-concept, and self-esteem when measured cross-sectionally (78–81). Among individual clinical factors, seizure frequency appears to contribute the most to ratings of severity of epilepsy (65). During the early stages of the disease, having frequent seizures has been found to be associated with depression in adolescents with varying disease durations (82,83). Thus, the exploration of severity of epilepsy in the early years of the disease as a risk factor for subsequent depression among young people with childhood-onset epilepsy seems

warranted. Sections 2.2.1 to 2.2.5 are a review of the clinical features of epilepsy (severity of seizures, frequency of seizures, AED use, seizure type, duration of epilepsy, and age of onset) indicative of severity of epilepsy that have been found to be associated with depression.

2.2.1 Severity of Seizures and Poor Seizure Control

Severity of seizures and severity of epilepsy are highly interrelated and are occasionally incorrectly used interchangeably. The severity of seizures is only one of several determinants of overall severity of epilepsy. Severe seizures may be difficult to control so may lower autonomy, have psychosocial implications, and decrease quality of life (84,85). As such, severity of seizures has been a well-studied risk factor for depression in people diagnosed with epilepsy (78,84,86–88). A population-based study in the UK of children and adolescents with epilepsy has been the only one to find increasing seizure severity to be independently associated with a higher risk of depression (OR= 1.09, 95% CI =1.01 to 1.17) (78). The mean age of epilepsy onset within this group was 6 (SD: 4.83) years and all participants were prescribed antiepileptic medication within the last six months. Due to the cross-sectional nature of the study, the direction of the relationship between increased seizure severity and depression cannot be determined.

Lack of seizure control is more common in those with more severe seizures and has been found to be associated with the risk of depression in a small number of studies. Among adults (n=300), effective seizure control was associated with a reduced risk of depression, measured using the Hospital Anxiety and Depression Scale (HADS) (89). Moreover, uncontrolled seizures posed a 2-fold increase in the risk of having major depression in 15 to 85-year-old epilepsy patients (n=298) (90). Consistent findings were obtained for a similar outcome of major depressive disorder (MDD) for children and adolescents (91). The participants (n=174) in this study had a mean onset of epilepsy of 5.6 years and were prescribed AEDs for a minimum of 6 months prior to study enrollment. MDD was assessed using the Schedule for Affective Disorder and Schizophrenia for School Age Children: Present and Lifetime Version.

2.2.2 Frequency of Seizures

Experiencing frequent seizures while using AEDs is an indicator of poor seizure control and worse disease severity, making it a potential risk factor for psychosocial consequences. A high frequency of seizures has been found to be associated with a number of psychiatric problems including depression, anxiety, low self-esteem, and stressful life experiences (92–96). Although the findings of seizure frequency being a risk factor for depression are mixed (87,88,97–99), a large number of studies have reported that the two variables are significantly related (82,83,90,91,100–106).

The definition used to classify frequent seizures is highly variable among studies, ranging from experiencing seizures on a daily basis to experiencing any seizure in the past week, month, or year. One study compared the frequency of seizures that people over the age of 16 (n=440) had in the past 2 years (none, once, more than once but not monthly, monthly to weekly, at least weekly) and found this to be the only epilepsy-related risk factor for depression, measured using the Center for Epidemiological Studies Depression Scale (CES-D) (100). A key limitation that may explain the lack of associations between other epilepsy-related variables and depressive symptoms is that participants reflected only those who attended a primary care clinic potentially under-representing severe cases.

Having seizures more than once per month more than doubled the risk of depression in a study of adults with epilepsy (101). However, this study did not include all seizure types; specifically, people experiencing tonic, atonic, clonic, or atypical absence seizures were excluded. Adults who experienced one to three seizures monthly were approximately four times more likely to have depression compared to those who did not have a seizure every month (102). Among adolescents with childhood-onset epilepsy, the frequency of seizures in the preceding month was the best predictor of depressive disorders and also of anxiety, measured using the Diagnostic Interview for Children Version IV (103). Another more recent study obtained consistent findings, however their outcome of interest was exclusively MDD (91). Youth with seizures occurring more than once a week were also more likely to have an episode of MDD compared to youth with a lower frequency of seizures. Furthermore, a study found that patients who had a seizure at least once a week were three times more likely to have depression, assessed

using the HADS, as compared to patients who were free of seizures for the past year (104).

Seizures in the past six months were defined as frequent seizures among studies with exclusively adult participants. Having at least one seizure in the past six months was associated with a high risk of depression (RR= 1.39, 95% CI=1.12 to 1.74), assessed using the Hamilton Depression Scale, for women between the ages of 18 to 55 years (105). Additionally, a two-fold increase in the Neurological Disorders Depression Inventory for Epilepsy score was found among adults with epilepsy who reported at least one seizure in the past six months as compared to those with no seizures (90). Using the Patient Health Questionnaire-9 to assess depression, another study found that adults with seizures in the past six months with a loss of consciousness had a higher risk of depression (OR=5.60, 95% CI= 2.54 to 12.77) compared to those with no loss of consciousness (OR= 2.22, 95% CI= 1.06 to 4.66) (n=80 cases and 141 controls) (106).

Among children and adolescents, a high frequency of seizures close to epilepsy onset has also been examined as a risk factor of future depression. Among children (n=25) with idiopathic epilepsy and a disease onset before 15.6 years, Children's Depression Inventory (CDI) scores were higher in those with daily seizures than those who had one seizure or were seizure free after using AEDs in the early stages of the disease (83). Among adolescents (n=140) with an epilepsy onset between the ages of 0.3 and 17 years, frequent seizures (weekly or daily) at the time of onset were associated with the risk of having depression (OR=3.52, 95% CI=1.51 to 8.17, p =0.003), assessed using the HADS (82).

2.2.2.1 Seizure Remission

Although epilepsy is an incurable but controllable disease, researchers sometimes classify patients as being in remission and or having inactive epilepsy if they have been seizure free for years to reduce disease-related stigma (1). There have been varying definitions of how many years of seizure freedom are required to be in remission with some proposing that it should be five years (107). Being in remission is different, however, from epilepsy being 'resolved'. In the 2017 ILAE guidelines, a patient's epilepsy is considered resolved if he/she had age-dependent epilepsy and are now past the applicable age or if the patient

has been free of seizures for the past 10 years and has not used an AED in the last 5 years (108).

Although it is assumed that gaining remission would reduce the likelihood of epilepsy-related stigma, this is not always the case (109). A prospective study that followed adolescents for eight to nine years after diagnosis of childhood-onset epilepsy found gaining remission (five years of seizure freedom) was not associated with child-reported health related quality of life but rather having a psychiatric illness was of greater importance (110). However, among this same cohort of adults, five years of seizure freedom was associated with a greater proportion of people reporting internalizing disorders (111). Among Canadian adults, experiencing even a single seizure in the past five years has been found to lead to a six-times greater odds of having depression as compared to those who achieved five-year seizure freedom (112). Failure to achieve five-year seizure freedom was also associated with a greater risk of being unable to drive; experiencing limitations for education, employment, and activities of daily living; and having greater self-perceived stigma (112). Seizure remission has also been found to reduce illness intrusiveness and the severity of subjective handicap that epilepsy places on patients' daily activities (113,114). One study that classified adults as being in remission if they had not experienced a seizure in the past year found that 4% of people in this group had depression as compared to 17% of people with active epilepsy. This trend was also apparent with anxiety where 28.9% of people with active epilepsy had anxiety as compared to 12.4% of people in remission (115). Alternatively, one study found neither seizure freedom nor any other epilepsy-related clinical factor to be associated with psychiatric disorders (116). Gaining seizure remission was also not found to effect social outcomes, but rather having a mental handicap and/or learning disorders were more influential (117).

2.2.3 Antiepileptic Medication

Antiepileptic drugs (AEDs) may exhibit mood-altering properties and thus, have been examined as risk and protective factors for mental illnesses (118). Occasionally, patients with less severe epilepsy do not require AEDs, others experiment with different combinations to gain full control of their seizures, and a select few are unsuccessful at

controlling their seizures with AEDs (119). Drug responsiveness has been found to decrease the risk of major depression among adults (OR=0.23, $p<0.01$), measured using the Diagnostic and Statistical Manual of Mental Disorders and confirmation from a hospital psychologist (120). Non-compliance to medication may be a problem area for people with depression as there is a higher occurrence of MDD in patients with poor medication adherence as compared to those with high or medium adherence rates (91). The presence of side effects of AEDs is also associated with depression, assessed using the HADS, among adults (n=1069) with epilepsy (92). Participants who experience medication side effects are approximately three times more likely to experience depression (AOR=3.07, 95% CI= 1.80 to 5.21) as well as anxiety (AOR=2.51, 95% CI= 1.60 to 3.94) (104).

The majority of studies have reported that AED type is not correlated with depression (97). Nonetheless, a small number of studies reported an association between these two factors, each with different AEDs being problematic. The AED lamotrigine has been found to decrease the likelihood of being depressed (OR=0.4, 95% CI= 0.2 to 0.8) among adults from a tertiary care centre (106). Alternatively, phenobarbital has been found to be associated with a higher risk of depression among children who had a family history of depression (121). Oxcarbazepine use, which was found to be correlated with frequent seizures, polytherapy treatment, and complex partial seizures has been found to be associated with an increased risk of depression as compared to other AEDs (OR= 2.26, 95% CI=1.04 to 4.90) (101). This study further explored the effect of drugs by grouping together medications thought to have depression-inducing properties, including hormones, β-blockers, calcium antagonists, interferons, and some antiparkinsonian drugs, and found depressogenic medications to be related with a risk of depression in PWE (OR= 3.33, 95% CI= 1.50 to 7.39, p=0.003).

2.2.3.1 Monotherapy vs. Polytherapy

In more severe cases of epilepsy, the use of a single AED (monotherapy) is not sufficient to control seizures and multiple AEDs (polytherapy) are required (119). The findings on whether the use of more than one AED places PWE at greater risk of developing depression are inconclusive (122–124). Among adults who had childhood epilepsy, a

history of failing to achieve seizure control from two or more AEDS was not associated with psychiatric illnesses (111). The majority of studies, however, found monotherapy to be the safer treatment option with regards to the risk of psychopathology. Nonetheless, when seizures cannot be controlled with only one AED, polytherapy treatment is unavoidable. In a systematic review, four studies were identified where polytherapy was significantly associated with higher depression scores in children and adolescents, with one study finding them to be associated with the following domains of the CDI: interpersonal problems, ineffectiveness, and negative self-esteem (122). The findings are consistent in adults with one study showing almost a two-times greater risk of depression with polytherapy treatment (COR= 1.76, 95% CI= 1.11 to 2.78) as compared to montherapy treatment (90,94,102). Another study found that a higher number of people had depression if they were not only using more than one AED but also using a clonazepam drug (88).

2.2.4 Seizure Type

The prognosis for epilepsy may be related to the type of epilepsy syndrome (68,125) but, it is difficult to determine if certain types of seizures are predictive of more severe epilepsy. As such, there has been plenty of research comparing types of seizures as predictors of depression. The majority of studies are in agreement that the laterality of where seizures originated and thus epilepsy type is not associated with the risk of depression (50,82,83,87,97,105,123). Nonetheless, there have been few studies with opposing results in samples spanning all ages. A systematic review that included a total of 1095 children and adolescents aged 4 to 19 years with epilepsy identified four cross-sectional studies where focal epilepsy was associated with depression to a higher degree than generalized epilepsy (123). Symptomatic focal epilepsies, specifically, have been found to be independently positively associated with depression, as measured by the Beck Depression Inventory (93). This study included patients aged 1 to 60 years with a mean age of epilepsy onset of 13.9 (SD= 9.5) years who had no history of status epilepticus for 6 months prior to study entry. Another study (n=90) had slightly differing results, concluding that both generalized and focal epilepsy types are risk factors for depression as compared to undetermined epileptic seizures (126). Their results may have limited

external validity given they had a much larger proportion of undetermined seizure types than is found in the general population. Conversely, one study found that children (n=48) with generalized seizures self-reported more depressive symptoms, as measured by the CDI, but this finding did not hold for the parent reports of their child's depression (127).

Among hospitalized and/or ambulatory care patients (n=117 females and 85 males) between the ages of 18 to 50 years with epilepsy, depression was more common in those with complex partial seizures and less common in those with secondary generalized tonic-clonic seizures (124). Tonic-clonic seizures, specifically, have been found to be associated with the anhedonia subscale of the CDI among children (96). Complex partial seizures were also found be a positive clinical risk factor for depression (OR=0.112, p =0.002) in patients aged 15 to 71 years (128). The number of seizure types was the strongest predictor of depression in their study (OR= 3.77, p =0.049). A notable study limitation is that their patients were from a tertiary epilepsy center, which may have led to an overrepresentation of severe cases. There was further support for partial seizures as a risk factor with another study finding that patients with partial seizures more frequently reported having depressive systems, identified by the Hamilton Depression Rating Scale, compared to patients with generalized epilepsy in their sample (n=116) with an age range spanning 16 to 70 years (88).

2.2.5 Duration of Epilepsy and Age of Onset

Early severity of epilepsy in some cases may predict the overall duration of disease and whether the child will ever outgrow it (129). Likewise, age of seizure-onset is associated with the type of epilepsy syndrome that may, in turn, be associated with disease prognosis (130,131). Although disease duration and age of epilepsy onset are not direct predictors of the early severity of epilepsy, they are important clinical factors to explore as risk factors for depression. The majority of studies are in agreement that age of epilepsy onset is not related to depression (50,83,86,88,91,122–124,128) but the findings on the relationship between duration of epilepsy and depression are inconclusive (91,104,122–124,128). A comprehensive review (122) identified only two studies that found a significant relationship between both these epilepsy-related factors and depression in youth (82,87). One found both age of epilepsy onset and disease duration to

be specifically related to the interpersonal domain score of the CDI (87). In addition to both being predictors of depression, a younger age of onset was also significantly associated with feelings of stigma among a community-based sample of adults with epilepsy (132). The median age of onset in this sample was 22 (range=86) years with 43% of the sample having an onset before the age of 19.

In addition to being a risk factor of depression, a longer duration of epilepsy is associated with the prevalence of MDD and anxiety in children and adolescents (82,83,91). Duration of disease is also associated with depression in adults with one study finding that having epilepsy for more than a decade increased the chances of having clinically significant depression symptoms (52 cases and 52 controls) (OR= 6.21, 95% CI= 1.66 to 23.32), assessed using the HADS (98,102). When comparing adult outpatients (n=116) who had mild to severe depression, those in the moderate depression group, identified by the Hamilton Depression Rating Scale, had the longest disease duration (88).

2.3 The Importance of Family Environment in Childhood Epilepsy

Childhood chronic diseases not only negatively impact the person with the disease but also their families (133). In the case of epilepsy, disease onset has been shown to bring up parental feelings of the 'loss of a perfect child' and that their child may always be different than other children (133,134). The progression of the illness further exacerbates problems by increasing feelings of frustration, hopelessness, depression, anger, and guilt among family members (135). Over the course of the illness, changes in family relations may occur due to the disease prognosis, the attached social stigma and/or the increased focus of parents on their child with the health condition leading to a decreased focus on their other children (133). As such, siblings of children with chronic epilepsy have been found to have higher rates of psychiatric disturbances as compared to those with newly diagnosed siblings (136).

Childhood chronic illnesses increase the child's dependency, required long-term care, family restrictions, and places an overall burden on the family (137). Along with

regular parental duties, parents have the additional responsibilities of managing their child's condition and any consequences that may arise as a result, including school absences and lower grades. Thus, the family dynamics are forced to change to accommodate the needs of the illness (138). Unfortunately, these modifications in family processes triggered by the onset of the illness are sometimes associated with worse medical outcomes in the child with the condition (138). This may be due to families adapting poorly to the disease leading to a stressful family environment (139,140). In fact, the continued treatment of epilepsy has been found to increase the risk of maladaptive responses by both the child and his/her family (141). Consequently, families of children with a chronic illness are at a higher risk of developing psychological problems as compared to their counterparts (142).

It is imperative that families adjust well to their child's chronic illness as it is presumed to influence how the child adapts (143). Poor family adaptation is likely to increase the risk of poor child adjustment and in turn, the child is likely to experience emotional or behavioural problems (140,144). However, due to the unpredictable nature of epilepsy and the fears associated with seizures, there is an increased risk of parents becoming over-protective and emotionally over-involved with their child (87,145). Resources such as extended family social support, financial efficacy, and family mastery have all been found to aid in parental adaptation to their child's illnesses or disability (140,146).

2.4 The Impact of Severity of Epilepsy on the Family

The severity of childhood epilepsy, characterized by a number of illness features such as frequency and severity of seizures, is likely to affect how the family reacts to the disease. Although no study has examined the direct impact that the overall severity of epilepsy has on aspects of the family environment, a number of studies have found clinical features of epilepsy to be related to family factors. One study found that stress within families was higher in those with children who experienced more frequent seizures compared to those with infrequent seizures or no chronic illness (147). Siblings of children with frequent seizures expressed more concerns about their sibling's epilepsy as compared to siblings of children with infrequent seizures (147). Frequency of seizures in

children and adolescents has also been found to be associated with an increased risk of parental anxiety (148). Additionally, mothers of children with frequent seizures have been found to exhibit more over-controlling, anxious, and demanding attitudes (149). Mothers whose children with epilepsy fail to gain full control of their seizures have a higher risk of trait anxiety (149). A opposing study found no difference in the risk of parental anxiety based on the level of seizure control or seizure type (150).

Comorbid problems such as cognitive deficits are common in people with epilepsy, with those who have more severe epilepsy being at higher risk (151). Children with epilepsy and no comorbid conditions tend to have less anxious mothers as compared to those with mild, moderate, or severe disabilities (150). Mothers of children with epilepsy who suffer from motor or 'mental retardation' have a higher problem-solving deficit, i.e. lower ability to resolve problems, compared to mothers of children with no epilepsy or comorbidities (149). Furthermore, a longer duration of epilepsy has been found to be associated with problematic family functioning and authoritarian maternal parenting behaviours signified by over-punishing and rigid parental attitude (149). Longer disease durations may be indicative of resistant and/or more severe epilepsies as many people with childhood epilepsy outgrow it (74).

2.5 Family Factors and Youth Depression

A family's expectations and attitudes towards epilepsy are strong predictors of long-term psychological adaptation in individuals with epilepsy (137). Evidence suggests that family factors may have an even greater influence on child psychological adjustment to epilepsy than clinical factors (152). A recent study found depression in adolescents with epilepsy to be attributed to their negative attitudes regarding their condition and their family situations, rather than directly being a result of seizure or syndrome type or seizure intensity (153). A second study found family functioning to be the second most important predictor of child adjustment after pharmacological factors with other epilepsy-related characteristics being of lesser significance (154).

Although the importance of family environment in childhood epilepsy is well known, its role as a predictor of psychopathology in children with epilepsy is now

increasingly being recognized and incorporated into epilepsy research (155). The findings of a few studies indicate that caregivers' response to epilepsy and their relationship with their child may be important in lowering the risk of depression in youth who have epilepsy. Particularly, poor quality of the child-parent relationship and parental rejection have been shown to be associated with a higher risk of psychopathology in the offspring with epilepsy (155). Parents' lack of confidence in managing their child's condition and parental over-control are also risk factors for psychopathology and depressive symptoms, respectively (156,157). Furthermore, large discrepancies between a mother and father's ratings of negative coping behaviours by their child with epilepsy was related to children's depressive symptoms, measured using the CDI, and to poorer self-concept (80). This finding indicates that when two parents have different perceptions of their child's coping, the child is at an increased risk of psychiatric illnesses. These differences in perceptions may be attributed to a number of factors including child-parent interaction patterns and different parenting styles within a set of parents (80).

It is plausible that depression among primary caregivers can increase the likelihood of depression in their offspring. This may be attributed to a number of phenomena including the hereditary nature of depression, depression in parents resulting in negative parenting behaviours, or a shared stressful family environment resulting in mental health problems in all family members (158). Among adults with epilepsy (mean age of nearly 25 years), the most important risk factor for depression was their caregiver having depression (94). Other familial factors such as the caregiver's education level, perception of burden and stigma, and level of family functioning were only correlated with depression in PWE through the meditational effects of the caregiver's depression. Thus, it may be vital to diagnose and treat depression in parents early on to reduce its effect on the caregiver's ability to nurture their child with epilepsy.

Rodenburg et al. (2005) reviewed the literature on family factors as risk factors for psychopathology in children with epilepsy and found the contextual factors of family stress, family functioning, and family resources to be important predictors of child psychopathology, mainly depression. With the increased stress that epilepsy places on the family it is likely that the entire family would be affected, leading to them experiencing difficulties with functioning and cohesion (159). To cope with the epilepsy-associated

demands, adequate family resources are required as they are deemed essential for better psychological adjustment in children with chronic conditions (160). As both family functioning and resources may be more amendable to change compared to clinical factors, targeting them with effective family-based interventions may reduce the risk of psychiatric problems in youth with epilepsy (154,159).

Although studies indicate that family factors may be associated with youth depression among those with epilepsy, the specific role of these factors and how they interact with the clinical features of epilepsy is generally unknown. It is plausible that family factors may play an intermediary role between clinical factors and mental health outcomes. Findings from past studies suggest that family reactions, behaviours, and circumstances may potentially mediate the physical manifestation of epilepsy and behavioural and emotional outcomes of family members (133). One study found that the effect of seizure severity on children's depressed mood was 'completely mediated' by parent's level of perceived stigma (161). In another study, the effect of epilepsy on depressed mood was rendered non-significant when controlling for family processes including restricted activity days, perceived life-threatening illness, and poor general health (157). These studies are limited by the fact that they did not test the significance of the indirect effect (path from exposure to outcome through the mediator). Furthermore, the potential mediating effects of family factors have not yet been examined, especially in the case of depression, representing an important target for future research.

One review concluded that most illness-related variables were not associated with psychological and adaptation problems in children with less severe epilepsy and those with adequate seizure control (152). However, illness-related variables were important risk factors for psychopathology in children with severe epilepsy and those with poor control of their seizures. As such, the effect that epilepsy has on negative psychiatric problems may be based on severity of epilepsy. In agreement with other researchers, the authors determined that family variables, the influence of epilepsy on family life, and the family's ability to cope with stress are factors that are likely to mediate the relationship between illness factors and psychopathology in children with epilepsy (152).

Building on previous work and suggestions for future studies by researchers in this field, the current study examines family factors as mediators in the relationship

between severity of epilepsy and depressive symptoms. Below is a review of research on the three family factors selected for this study [family functioning, family resources (family mastery and health and extended family social support), and parental depressive symptoms] as potential mediators.

2.5.1 Family Functioning as a Mediator

Although epilepsy can result in psychosocial problems in the person with the disease, it also affects their family members and consequently their overall family system. Thus, it is not surprising that families with a child/adolescent who has epilepsy experience poorer family functioning (general functioning, affective responsiveness, affective involvement, behaviour control, problem solving, and communication) as compared to families of children without epilepsy (162). Families of children with epilepsy as compared to those with diabetes or no chronic illness also have poorer family cohesion and quality of parent-child communications (163,164). Another study had consistent findings when comparing children who have epilepsy with those who have another chronic disease such as asthma and found children with epilepsy to be less satisfied with their family functioning (165). However, when these same children became adolescents they were no more dissatisfied with their family relationships compared to adolescents with other chronic diseases (79). Level of maternal satisfaction with family functioning also did not differ between families of children with epilepsy or those with asthma (140).

Although studies have found poorer family functioning in families with a child with epilepsy, whether the effect of epilepsy on family functioning varies by disease severity, has not been examined. Individual aspects of epilepsy that characterize higher disease severity have been linked to poorer family functioning, however. First, longer disease duration was found to be associated with poorer family functioning scores particularly in the areas of problem solving, communication, affective involvement, behaviour control, and general functioning among children and adolescents who had epilepsy with a disease duration ranging from 2 to 144 months (149). Among children with intractable epilepsy, frequency of seizures has been found to be inversely associated with poorer family cohesion (154). Lastly, mothers of children who had epilepsy along with comorbid behavioural problems reported poorer family functioning compared to

those whose had epilepsy alone (140). Having comorbid chronic illnesses was found to lower family functioning which, in turn, led to experiencing poor psychosocial functioning among adolescents and young adults with epilepsy (166). In this study poor psychosocial functioning was defined as having poor quality of life along with high depressive symptomology and anxiety (166). Therefore, it is plausible that family functioning may play a mediating role in the relationship between severity of epilepsy and youth psychopathology.

A number of studies have reported a relationship between family functioning and depression in PWE. Children who have epilepsy and clinically significant depressive symptoms reported experiencing greater family conflict within the past year as compared to those without depression (121). However, approximately two years later, family conflict in this small group of children (n=28) improved, suggesting that a family's response to their child's epilepsy is not static but evolves over time (167). Mothers of children who had depression reported poorer family functioning compared to those whose child with epilepsy did not have depression (140). Among youth with childhood-onset epilepsy, dissatisfaction with family functioning has also been found to be associated with depressive symptoms (80,168). Family functioning has also been found to be associated with depressive symptoms in mothers of adolescents with epilepsy (94). In this study, family functioning was indirectly associated with adolescent internalizing and externalizing problems through parental depressive symptoms and the level of rejection a child felt towards his/her parents (94). Family functioning has also been found to partially mediate the relationship between parental depressive symptoms and child health related quality of life (169). Likewise, family functioning has been found to mediate the relationship between behavioural problems and emotional well-being and moderate the relationship between cognitive decline and self-esteem in children with epilepsy (170,171).

2.5.2 Family Resources as a Mediator

Families vary in the level of resources they have available to them to assist them in coping with stressful situations such as the care of a child with a chronic disease. Family resources have been found to be more problematic for families of children with epilepsy

compared to those with other chronic illnesses (140). For the purposes of this study, family resources do not refer to financial assets but rather the concepts of extended family social support and family mastery and health. Having sufficient social support is critical for families when adapting to a chronic illness and has been found to be associated with depression, irrespective of the level of stress in adults with epilepsy (99). Specifically, familial social support provided by extended family has been found to reduce the risk of depression in mothers of adolescents with epilepsy (172).

Several studies have found deficits in various aspects of family resources to be associated with poor psychiatric health. The findings of one study indicated that families with fewer resources are more likely to have children with poor psychosocial adaptation (140). They found scores in all four subscales (esteem and communication, mastery and health, extended family social support, financial well-being) of the family inventory of resources for management (FIRM) to be significantly lower for children with depression or behaviour problems as compared to those without depression or behaviour problems (140). Austin and colleagues (1992) replicated the initial study and found poor family mastery and extended family social support to be associated with behaviour problems in children with epilepsy in a subsequent study. Moreover, level of parent-reported adaptive family resources were inversely associated with the depression/anxiety subscale of the Child Behaviour Checklist-Youth Self Report in children with epilepsy but not depression alone as measured by the CDI (86). Contrary to these findings, among adolescents with epilepsy, adaptive family resources did not differ in those with or without depression and or those with or without anxiety (103).

A recent study found that improvement in neuropsychological functioning from seizure-onset to three years post-diagnosis was associated with reductions in symptoms of depression in children with epilepsy with better family mastery being a protective factor in this relationship (171). Consistent with this finding, two studies found the negative effect of parental depressive symptoms on child health-related quality of life and child emotional well-being, to be moderated by level of family resources (169,170). Although it is possible that family resources may be a moderator of the relationship between severity of epilepsy and patient psychopathology, it is also possible that it could be a mediator. A recent study found family resilience, a measure of family mastery, to

significantly mediate the relationship between severity of epilepsy and self-esteem in youth aged 13 to 16 years old (n=153) (81). Youth with more severe epilepsy reported poorer family resilience, and in turn, had lower self-esteem as compared to those with moderate-low disease severity.

To determine the casual order of the relationship between family resources and patient psychopathology, a study examined whether family resources are predictive of internalizing problems over time (156). They assessed whether family mastery at the time of seizure-onset is predictive of internalizing problems, i.e. depression and anxiety, two years post-diagnosis (156). They found that at baseline and at the two year-follow up, family mastery was negatively associated with total behaviour problems, internalizing, and externalizing problems. Baseline family mastery was significantly negatively associated with increases in total, internalizing, and externalizing behaviour problems from baseline to two years. Thus, family mastery predicted behaviour problems over time with those who had higher baseline levels of family mastery showing improvement in child behaviour problems (156).

2.5.3 Parental Depression as a Mediator

Diagnosis of a chronic illness has been found to be associated with depression among caregivers (173). This may be attributed to the increased burden placed on caregivers and the hours they spend caring for their dependent with the burden only increasing the longer the time since diagnosis (173,174). Parental depressive symptoms are problematic for growing children as they are likely to reduce the quality of the parent-child relationship. Maternal depressive symptoms have been found to be positively associated with uncertainty regarding their child's epilepsy and boundary ambiguity (child's role in the family) and so may reduce the quality of care the child receives (175).

A systematic review found that mothers of children with epilepsy have high rates of depression with prevalence of depression ranging from 12% to 49% across six studies (176). A large portion (31.5%) of mothers of children with epilepsy seem to have a MDD (177). The prevalence of depression and anxiety in mothers of children and adolescents with epilepsy has been found to be significantly higher than that of mothers of healthy children without epilepsy (86,149). Findings are mixed, however, as other studies found

no difference in the risk of depression between mothers of children with epilepsy and mothers of children without epilepsy or another chronic disease (178,179).

Clinical factors indicative of more severe epilepsies have been examined as risk factors of parental depression. The presence of 'mental retardation' in children with epilepsy, which is likely reflecting more severe epilepsy, was found to be associated with lower maternal educational attainment and an increased risk of maternal depressive symptoms (180,181). However, children having a learning disability and their fathers' level of education were not associated with the risk of paternal depression (182). A longer duration of epilepsy was also not associated with depression in either mothers or fathers (181,182). Severity of epilepsy in children was found to be associated with paternal depression one year post-diagnosis, however, the sample was too small for the findings to be considered conclusive (n=11) (183). In this sample, fathers of children with generalized seizures appeared to have more depressive symptoms 24 months post-diagnosis as compared to those with partial seizures (183).

There are mixed findings on whether past or current parental depression is associated with depression in youth with epilepsy. A review by Otero (2009) concluded parent's psychopathology to be one of the most important family factors influencing child psychological problems. In children with epilepsy, a family history of psychopathology has been shown to be a risk factor for depression (184). In a hospital outpatient sample of adolescents with epilepsy, parental psychopathology was found to be associated with depressive disorders in youth (103). Parental depression was also found to be associated with internalizing and externalizing behaviour problems in children and adolescents (155). However, two other studies did not find maternal depression to be correlated with children's and adolescent's risk of depression (86,178). In samples of people with more severe epilepsy, the results of all studies are consistent finding parental psychiatric illnesses to be predictive of psychiatric illnesses in their offspring. Among children with chronic or difficult to control epilepsy, a past history of maternal psychiatric treatment was found to be correlated with an increased risk of patient emotional and behavioural disturbances (141). In a previous study, Hoare (1984) also found past psychiatric illnesses in mothers, but not in fathers, to increase the risk of psychiatric illnesses in children with chronic epilepsy.

A number of studies have found parental depression to be associated with both the severity of epilepsy and youth psychiatric illness. Thus, it is plausible that parental depressive disorders may mediate the effect of severity of epilepsy on the risk of youth depressive disorders. One study found parental anxiety/depression to be significantly more common in parents of children who had more seizures and/or behaviour problems (185). More depressive symptoms in mothers of children with epilepsy were found to not only be associated with greater severity of illness and more child behaviour problems but also with maternal perceptions of greater stigma, dissatisfaction with family relationships, less extended family social support, and lower family income (172). Lastly, among children and adolescents with intractable epilepsy, behaviour problems and attention problems were found to be correlated with maternal depression but family income was not (186).

2.6 Limitations of Previous Studies

With depression being a common negative outcome in PWE, many studies have assessed its risk factors. However, it is also essential to establish how risk factors work together to create pathways in which depressive disorders may arise. This in turn will help establish targets for interventions to reduce the effect of less amendable clinical factors on the risk of depression. For example, family factors are related to psychiatric disorders in epilepsy patients and may be potential targets for supports but have yet to be explored as intermediary variables between clinical factors and depression.

The casual relationships between risk factors and depression have not been explored since nearly all previous studies have been cross-sectional, measuring the exposure and outcome at the same time. Shortage of prospective studies has also made it difficult to incorporate clinical factors near onset as predictors of subsequent depression. Furthermore, the majority of studies have focused on assessing the individual effects of each clinical factor, as opposed to exploring their combined effect that forms overall severity of epilepsy, in turn, causing psychiatric illnesses. As no single clinical factor has been established to be a predictor of psychopathology in PWE, it is likely that the effect that epilepsy has on causing negative psychosocial outcomes is based on overall disease severity. Lack of examination of disease severity as a risk factor for mental illnesses may

have been attributed to the absence of a validated measurement tool to feasibly assess severity of epilepsy; this has become available in the past decade (65).

Studies to date have employed a wide variety of samples, some of which are highly unrepresentative of the general population of PWE. Many studies recruit their participants from speciality care clinics and may have excluded milder cases of PWE. However, individuals with well-controlled/less severe epilepsy may still experience negative side effects such as the stigma that accompanies the disease and should be included in study samples (187). The vast majority of studies that included adults did not single out young adults, although the risk of depression in this age group may differ due to different stressors in this life stage as compared to middle and older aged adults. Furthermore, people who have been in remission for many years and thus have not had an epilepsy-related medical visit are excluded in many study samples. It is important to include this subgroup of people as having a chronic condition during their childhood is likely to have an impact on their long-term psychosocial health. There may also be common biological mechanisms related to epilepsy that places patients at a higher risk of psychiatric illnesses as compared to people who have never had epilepsy.

Chapter 3

3 Study Purpose, Objectives, and Conceptual Framework

This chapter will elaborate on the purpose of the study, state the objectives of this research, and provide information regarding the conceptual framework used to guide this project.

3.1 Study Purpose

The presence of childhood epilepsy may have long-term impacts on psychological well-being. Nonetheless, childhood clinical predictors of long-term outcomes such as depression have rarely been examined. The focus of past cross-sectional and longitudinal studies has been to assess the effect of each factor separately, with little attention to how these factors may come together to predict subsequent severity of epilepsy which, in turn, may lead to depression. The findings of these previous studies are inconclusive (reviewed in Chapter 2) warranting further research, particularly regarding the association between overall childhood severity of epilepsy and youth mental health disorders. Thus, this thesis aims to determine whether severity of childhood epilepsy early in the disease course is predictive of later depressive symptoms in youth.

Further, due to the multi-etiological nature of risk factors for depression and the established importance of family factors in childhood epilepsy (reviewed in Chapter 2), the role of family factors will also be investigated (133,159). Aspects of the family environment will be examined as potential mediating factors in the casual relationship between severity of epilepsy and depressive symptoms. To interpret these relationships, the stress process model has been selected as the conceptual framework to guide this research (refer to Section 3.3). Furthermore, as this is a long-term follow-up study, many changes may have occurred with regards to the clinical state of epilepsy. The current state of epilepsy is important to take into consideration as a number of cross-sectional studies have found epilepsy-related clinical factors that occur concurrently with depression to be associated with the risk of depression. Past severity of epilepsy may also be related to the future clinical manifestation of the disease, and thus current clinical factors will also be examined as mediators of the relationship between early severity of epilepsy and

subsequent depressive symptoms.

An important step in epilepsy research is to elucidate pathways by which negative mental health outcomes manifest, and to identify factors that are amendable to change through interventions. The examination of family environment may present an opportunity to counteract or minimize the risk of depression for youth by implementing family-based interventions. Examining severity of epilepsy in the early course of the disease will inform paediatric neurologists of its potential long-term implications for patients. Lastly, the examination of proximal clinical factors will help determine if past disease severity remains important or whether its effect is greatly reduced when accounting for the current clinical situation.

3.2 Research Objectives

The following are the research objectives to be addressed in this thesis:

1. To assess the association between early severity of epilepsy during childhood and subsequent depressive symptoms during adolescence and young adulthood, approximately a decade after diagnosis.
2. To assess whether aspects of the family environment (family functioning, family resources, parental depressive symptoms) play a mediating role in the relationship between early severity of epilepsy and subsequent depressive symptoms in youth.
3. To assess whether clinical factors (five-year seizure freedom, current AED use) play a mediating role in the relationship between early severity of epilepsy and subsequent depressive symptoms in youth.

3.3 Conceptual Framework

The stress process model was adopted as a theoretical framework to guide this research as presented in Figure 3.1 (188). According to the stress process model, stress occurs in two ways: the occurrence of discrete events and relatively chronic ongoing problems with the combination of both producing a synergistic effect on psychological well-being (188,189). In the past, social scientists have examined the impact of life events, ongoing life strains, coping behaviours, and social support networks and their influences on health

independently, although these processes all work together and should be examined as such (188). A key contribution of the stress process model is that it acknowledges the interrelationship among factors that affect mental health outcomes (188,190). It is a temporal framework where life stressors arise consecutively as the stress process unfolds to depict the causal relationship between exposure and outcome (188,189).

The stress process model consists of primary stressors that, in turn, lead to secondary stressors, stress mediators, and finally the stress outcome. Various studies testing this framework have used depression as their outcome of interest (188,191–193). Specifically, one study employed the stress process model to predict depressive symptomology and major depression in adults with socio-demographic factors as the risk factors, social support as the mediator and personal resources as the moderator (192). It has also been used previously in epilepsy research for the health outcomes of cognitive functioning, emotional wellbeing, and HRQoL among children and youth (169,170,194).

The diagnosis of epilepsy (primary stressor) and, in turn, living with epilepsy, where its effect is based on disease severity (secondary stressor), can lead to depressive symptoms (stress outcome). This relationship between severity of epilepsy and depressive symptoms may be mediated by a number of family factors/processes. The portion of the stress process model that this project aims to examine is how the secondary stressor (severity of epilepsy) leads to the stress outcome (depressive symptoms) via family mediators. The proposed stress mediators include family functioning, level of family resources, and parental depressive symptoms. Within the stress process model, mediators are coping or social support factors that produce variability in the outcome (188–190). Lastly, in this model, it is important to control for the background factors that describe the context of the stress through inclusion of the underlying characteristics of the subjects. The confounders in this project include: (a) demographic characteristics, such as child's sex, family income, and parental living arrangements; and (b) clinical risk factors of the exposure and outcome, such as behavioural problems, cognitive problems, seizure type, and age at diagnosis.

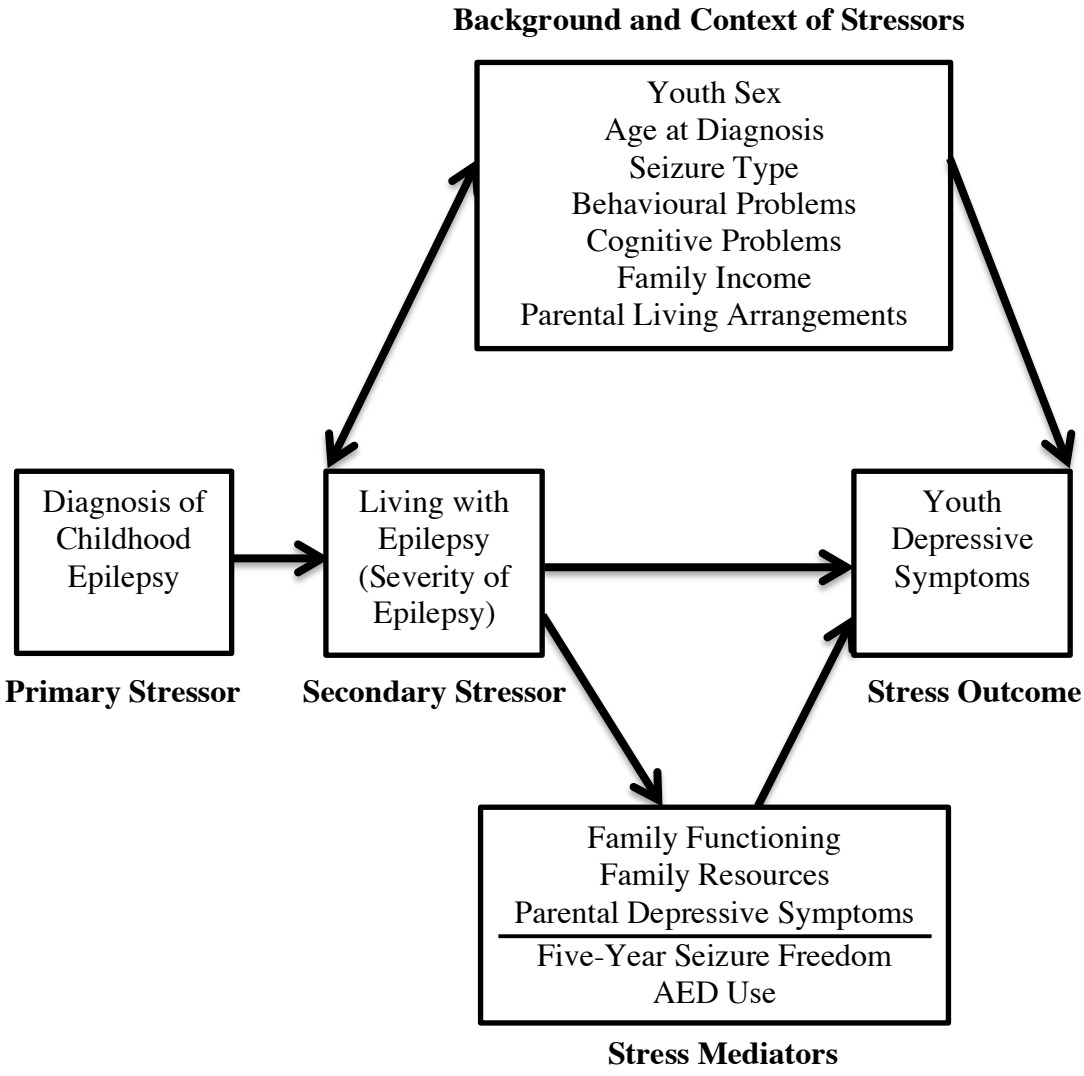

Figure 3.1: Conceptual Framework based on the Stress Process Model

Chapter 4

4 Methods

This chapter presents details of the data source used for this project, including the sampling methodology, data collection, and the measurement tools. In Section 3.3, the statistical methods used to analyze the data will be described. Finally, description of analyses conducted to reduce the risk of bias will be discussed including the attrition analysis and how missing data were handled.

4.1 Data Source

The data used for this study came from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES) consisting of the initial two-year follow-up study and the subsequent long-term follow-up study. HERQULES was a 10-year prospective study that employed a two-stage clustered sampling strategy to recruit children with new-onset epilepsy in Canada. In the first stage of sampling, all paediatric neurologists who were members of the Canadian Association of Child Neurology or were added to the sampling frame by a panel of experts were invited to participate in the study. A sample size of 72 members resulted, of whom 53 (74%) agreed to participate. Research ethics board approval was obtained from the 17 relevant research ethic boards across Canada.

The second stage of sampling consisted of the paediatric neurologists recruiting their eligible patients for the study based on the following inclusion criteria:

1. New case of epilepsy seen for the first time by a participating paediatric neurologist within the data collection period;
2. Age at first diagnosis between 4 and 12 years;
3. Parent/caregiver must have been primarily responsible for the child's care for at least the past six months before completing questionnaires.

Patients were excluded if they met any of the following criteria:

1. Previously diagnosed with epilepsy by another physician;
2. Diagnosed with other progressive or degenerative neurological disorder;
3. Diagnosed with other major non-neurological disorder that may impact their quality of life;

4. Parent/caregiver had insufficient English language skills to complete questionnaires.

The parents of eligible patients who agreed to provide their address were mailed a letter describing the study and explaining that they would be asked to complete four mailed questionnaires: baseline (post-diagnosis), six months, one year, and two years post-diagnosis. These questionnaires sought information on their child's HRQoL and their family environment, and would track changes in a number of factors over time. Parents were requested to provide informed consent for their child's neurologist to complete forms regarding their child's severity of epilepsy, seizure type, treatment and side effects at each follow-up. The parents' self-administered questionnaires took approximately 45 to 60 minutes to complete and were returned by mail, whereas the physician forms took 5 to 7 minutes to complete and were faxed back to the HERQULES office (Appendix A). Of the 455 eligible parents, 373 (82%) parents were successfully recruited and 282 (76%) were retained at the 2-year follow-up. The Tailored Design Method, which involves systematic follow-ups and reminders, was used throughout the HERQULES project in an effort to achieve good response rates (195).

For the subsequent long-term follow-up study, a letter of information was sent to invite parents and children over the age of 11 to participate to assess the current state of health of these youth and young adults (approximately 8 and 10 years post-diagnosis). Letters for the parents and their child explained that they would be required to complete two self-administered questionnaires, similar to the parent questionnaires in the original study, two years apart. The children had not previously completed questionnaires in the original study but were now old enough to self-report their health status. There were 220 youth eligible to fill out the questionnaires available as either web-based or paper questionnaires to increase participation rates (196). Research ethics approval was only required from the Western University Health Science Research Ethics Board for the long-term follow-up, given the established relationship with families from the initial phase of this project (Appendix D). Informed consent to contact and obtain information about the PWE's condition from their epilepsy care physician, if still receiving care, was obtained from the parents if the PWE was under the age of 16, both the parent and PWE if between

the ages of 16 and 18 and only the PWE if 18 years or older. Physicians, parents, and youth all received a token of appreciation for participating.

4.2 Measurement

Below is a description of how the exposure, outcome, mediators, and confounders were measured, categorized by respondent type (physician, parent, youth).

4.2.1 Physician Report

Severity of Epilepsy

The overall severity of epilepsy was measured using the Global Assessment of Severity of Epilepsy (GASE) Scale (65). This single item tool is designed for neurologists to rate their patient's overall severity of epilepsy. The question asked is "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". The options are as follows: (7) extremely severe, (6) very severe, (5) quite severe, (4) moderately severe, (3) somewhat severe, (2) a little severe, (1) not at all severe. The GASE has been found to have adequate construct validity, stability and responsiveness to clinical changes as well as good intra and inter-rater reliability (65,66).

Seizure Type

Physicians reported the epilepsy syndrome and types of seizures that the patient had according to the ILAE's classifications (primary generalized, absence, simple/complex partial, BECRS, secondarily generalized, BECRS + secondarily generalized and undetermined) (197,198). These two variables, seizure type and epilepsy syndrome, were used to compute a summary variable grouping the seizures broadly into generalized, partial or undetermined.

Behavioural Problems

Physicians reported whether patients had behavioural problems, rated the severity (mild, moderate, severe) and reported on diagnosed behavioural problems.

Cognitive Problems

Physicians reported whether patients had cognitive problems, rated the severity (mild, moderate, severe) and reported on diagnosed cognitive problems.

Age at Diagnosis

The age at the time of epilepsy diagnosis was determined based on the child's date of birth and the date of their first visit in which they were diagnosed by their paediatric neurologist participating in the HERQULES study.

4.2.2 Youth Report

Depressive Symptoms

Youth depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D)(199). The adult version was used as opposed to the child version, as it was age appropriate for the majority of youth and would allow for a consistent measure for the entire sample and across follow-ups (Appendix B). This is a 20-item scale that is designed to measure depressive symptoms in the general adult population over the past week. Respondents are asked to rate on a four-point Likert scale the number of days they felt a certain way ranging from 0 (rarely or none of the time/less than one day) to 3 (most or all of the time/5-7 days). The total scores range from 0 to 60 with a score of 16 or higher indicating that the person may be at risk of having a depressive disorder. The CES-D has been found to have high internal consistency, concurrent validity and construct validity in the general population (199). The CES-D had adequate internal consistency in our sample of youth with a Cronbach's alpha of 0.69.

Seizure Freedom

At the 10-year follow-up, youth were asked "When was your last seizure? (It is OK to provide your best guess)". The options were: less than 6 months ago, 6 months ago to less than 1 year ago, 1 year ago to less than 2 years ago, 2 years ago to less than 5 years ago, 5 years to less than 10 years ago, 10 years ago or more, I don't remember. In the event that youth did not report or did not recall how long ago their last seizure was, the value reported by their primary caregiver was imputed. This variable was dichotomized into

five years of seizure freedom being achieved or not achieved to handle the unequal size between intervals and to be comparable with past studies.

AED Use

At the 10-year follow-up, youth were asked “Are you currently taking any medication(s) to treat epilepsy or seizures?” and they responded with either “yes” or “no”.

4.2.3 Parent Report

Sex

The child’s sex was reported by their primary caregiver. They were asked “Is your child:” and were provided with two options: “Male” or “Female”.

Family Income

Primary caregivers were asked “In which category is your total yearly household income before taxes?”. At the 10-year follow-up, the income categories included: less than $20,000, $20,000 to $29,999, $30,000 to $39,999, $40,000 to $49,999, $50,000 to $59,999, $60,000 to $69,999, $70,000 to $79,999, $80,000 to $89,999, $90,000 to $99,999, $100,000 to $149,999, greater than $150,000. These income categories were collapsed into four categories of equal size: less than $50,000, $50,000 to $100,000, $100,000 to $149,999, greater than $150,000 due to a low cell count in half the categories and for ease of interpretation.

Parental Living Arrangements

Primary caregivers were asked “Are you currently living with a spouse or partner” with the two options provide being “yes” or “no”.

Family Functioning

Family functioning was measured using the Family Adaptability, Partnership, Growth, Affection and Resolve (APGAR)(200). This is a 5-item scale measuring perception of family functioning by examining satisfaction with family relationships in the five dimensions: Family Adaptability, Partnership, Growth, Affection and Resolve (Appendix C). For each dimension, respondents are to rate the frequency of satisfaction with family functioning on a three-point Likert scale ranging from 0 (hardly ever) to 2 (almost always). The scores range from 0 to 10 with a higher score indicating more satisfaction

with family functioning. In clinical and research settings, the Family APGAR has been found to be both valid and reliable (200–202). The APGAR had high internal consistency in our sample with a Cronbach's alpha of 0.88.

Family Resources

The extent to which families had resources available to help them adapt to stressful life events was measured using the Family Inventory of Resources for Management (FIRM) (203) (Appendix C). The two subscales included were Family Mastery and Health (20 items) and Extended Family Social Support (4 items) as they have been found to be associated with adaptation to childhood epilepsy (204). Respondents rate how each statement describes their family situation on a four-point Likert scale ranging from 0 (not at all) to 3 (very well). The FIRM has demonstrated adequate reliability and validity (203). The FIRM had adequate internal consistency in our sample with a Cronbach's alpha of 0.91 for the family mastery and health subscale and 0.64 for the extended family social support subscale.

Parental Depressive Symptoms

Parental depressive symptoms were measured using the same measure completed by the participating youth, the Center for Epidemiological Studies Depression Scale (CES-D) (199), described in Section 3.2.2 (Appendix C). The CES-D had adequate internal consistency in our sample of parents with a Cronbach's alpha of 0.74.

4.3 Statistical Analysis

All analyses were conducted using SAS software version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). Below is a description of the analyses conducted: descriptive, multiple linear regression, mediation and attrition analysis.

4.3.1 Descriptive Analysis

Clinical, familial, and demographic characteristics of the sample were described using frequencies and proportions for categorical variables, and means and standard deviations for continuous variables at each of the data collection points (baseline, 6 months, 1 year, 2 years, 8 years, 10 years). Bivariate regression analyses were conducted to assess which

factors were associated with the outcome without controlling for other factors. The following relationships were examined: the outcome (youth depressive symptoms) and the exposure (severity of epilepsy), the outcome and the mediators (family functioning, family resources, parental depressive symptoms, five-year seizure freedom, AED use), and the outcome and potential confounders (sex, age at diagnosis, seizure type, behavioural problems, cognitive problems, parental living arrangements, family income).

4.3.2 Multiple Linear Regression Analysis

A multiple linear regression analysis was conducted with youth depressive symptoms as the outcome to examine its relationship with the exposure (severity of epilepsy) while controlling for a number of clinical and demographic confounders. Potential confounders were sex, age at diagnosis, seizure type, behavioural problems, cognitive problems, parental living arrangements, and family income. The confounders were selected based on those factors that have been found to be predictors of depression in PWE and are likely to be associated with severity of epilepsy (41,78,82,87,88,93,97,123,126,132,205–208).

The outcome of interest, youth depressive symptoms, was measured at the 10-year follow-up. The exposure of interest, severity of epilepsy, was measured at the 2-year follow-up to allow physicians sufficient time to characterize the seizure type and try to arrive at whether an effective combination of drugs could be found to control seizures (74,77). The clinical confounders (seizure type, age at diagnosis, behavioural problems, cognitive problems) were measured at the 2-year follow-up, as they are highly associated with the exposure of interest. The demographic confounders (parental living arrangements, family income) were measured at the 10-year follow-up as they are likely to be more predictive of the outcome, depressive symptoms at 10 years, as compared to demographic characteristics around diagnosis. Additionally, these time points were selected to reduce the risk of intermediate confounding that may introduce bias when conducting the mediation analysis. Intermediate confounding may occur when the exposure is a causal risk factor of a mediator-outcome confounder (209,210). Lastly, the assumptions for linear regression (linearity, normality of residuals, lack of multicollinearity, autocorrelation, heteroscedasticity) were all met.

4.3.3 Mediation Analysis

Often in psychosocial research it is the case that a risk factor does not directly cause an outcome but it arises through a third or intermediary variable. This third variable is termed a 'mediator' and is a carrier of information along a casual chain (211). Figure 4.1 depicts the possible pathways between an exposure and outcome with and without the presence of a mediator (212,213). The total effect (c=ab + c') is the effect of the exposure on the outcome without taking the mediator into account. The direct effect is the effect of the exposure while controlling for the mediator (c'=c-ab) as if it were a confounder. Lastly, the path from the exposure to the outcome through the mediator is termed the indirect effect (ab) and is calculated from subtracting the total effect from the direct effect (c-c').

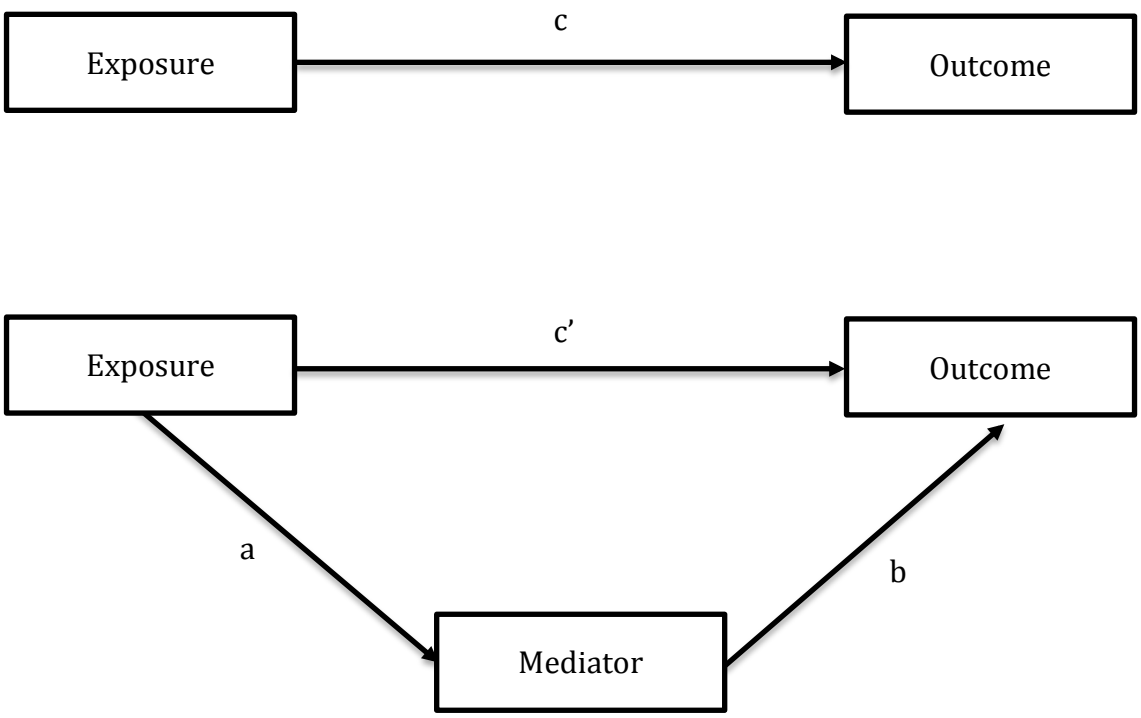

Figure 4.1: Mediation pathway

In this thesis, both family (family functioning, family resources, parental depressive symptoms) and clinical (five-year seizure freedom, AED use) factors were assessed as mediators in the relationship of severity of epilepsy and depressive symptoms. An important assumption of mediation is that the exposure is a predictor of the mediator and that the mediator is a predictor of the outcome (214). Thus, the family factors as potential mediators were measured at the 8-year follow-up to allow a temporal order between exposure, mediators, and outcome, a practice that is optimal when assessing casual relationships (215). Additionally, preliminary cross-lagged panel analyses and regression analyses were conducted to determine the casual order between severity of epilepsy and the selected family mediators (Appendix E). A cross-lagged panel analysis is used to determine the direction of the relationship between two variables measured at multiple time points in a longitudinal study. This is done by examining whether variable X at Time 1 and variable Y at Time 2 are associated or variable Y at Time 1 and variable X at Time 2 are associated (216). The results of these analyses found that severity of epilepsy was predictive of each of the family mediators (family functioning, family resources, parental depressive symptoms) and that these relationships were likely not bidirectional. The clinical mediators were measured at the 10-year follow-up due to the nature of these variables as they are more likely to be predictive of depressive symptoms and not vice versa. It is unlikely that depressive symptoms in the past week could cause five years of seizure freedom being achieved and/or AEDs being prescribed.

A rigorous method using generalized estimating equations (GEE) proposed by Schlucter (2008) was used to test mediation, i.e. the significance of the indirect effect. This method is based on the counterfactual framework where the influence of the mediator on the exposure and outcome relationship is assessed by observing the same individual at the same point in time with the mediator present or it absent. Thus, to apply this method, the data set must be duplicated as depicted in Table 4.1.

Table 4.1: Duplicated data set in preparation for GEE mediation analysis

ID	**Y**	**X**	**G**	**M***
1	y_1	x_1	1	0
1	y_1	x_1	0	m_1
2	y_2	x_2	1	0
2	y_2	x_2	0	m_2
n	y_n	x_n	1	0
n	y_n	x_n	0	m_n

The first set where the indicator variable (G) is equal to 1, the mediator (M*) is not present and thus is not adjusted for when examining the association between the exposure (X) and outcome (Y). This set may be fit to the following model:

$E(Y) = \beta_0 + \beta_1 X_1 + \theta_0 + \theta X$

$= (\beta_0 + \theta_0) + (\beta_1 + \theta)X$

In the second set, G=0 and thus the mediator is present and being controlled for in the assessment of the relationship between X and Y. This set can be fit to the following model:

$E(Y)= \beta_0 + \beta_1 X_1 + \gamma M$

The overall dataset created includes two copies per individual differing on whether the mediator is controlled for or not and is then fitted to:

$E(Y)= \beta_0 + \beta_1 X_1 + \theta G + \theta GX + \gamma M^*$

This model computes the difference between the coefficients from the full model (adjusted for the mediator) and the reduced model (unadjusted for the mediator), i.e. the indirect effect (θ). This is done in SAS software using the PROC GENMOD function which also computes the significance of the indirect effect using a robust "sandwich" estimator for the computation of the standard error. The validity of the GEE approach for different combinations of binary and continuous outcomes and mediators has been verified in a simulation study (217).

4.3.4 Attrition Analysis

An attrition analysis was conducted to determine whether the group of participants retained by the 10-year follow-up and those who did not participate in the 10-year follow-up differ in terms of any clinical, family, or demographic factors. The two groups of participants were compared on baseline clinical (severity of epilepsy, seizure type, cognitive problems, behavioural problems, age at diagnosis), demographic (sex, parental living arrangements, family income), and family factors (parental depressive symptoms, family resources, family functioning) using t-tests to compare means for continuous variables and chi-square tests and/or fisher's exact test to compare proportions for binary variables.

4.3.5 Missing Data

For a small number of patients where severity of epilepsy, seizure type, presence of cognitive problems or, presence of behaviour problems was missing due to physicians not having an opportunity to evaluate at the two-year follow-up, previously reported values for these variables were imputed where possible. For severity of epilepsy and seizure type, members of the research team reviewed all available study data, including when the youth's most recent seizure was; when AEDS were discontinued; communication between the study coordinator and the primary caregivers of children with epilepsy at the two-year follow-up; the type and etiology of seizures; and the trends in past and subsequent severity of epilepsy and seizure types. Imputations were not made where there was uncertainty regarding the risk of the previously reported type of seizures and severity of epilepsy changing. For cognitive and behaviour problems, all available study data including past history, trends and taking into consideration future reports on cognitive or behaviour problems was used. These future reports included both follow-ups with their physicians and parents reporting if their child ever had any cognitive (developmental delay, learning disability) or behaviour problems (conduct disorder, oppositional defiant disorder, attention deficit disorder and/or attention deficit hyperactivity disorder) at the 10-year follow-up. Imputations were not made where there was uncertainty regarding the presence of these comorbidities at the two-year follow-up.

Approximately 82% of the sample had no missing values for any of the variables after imputations using previous follow-up data was implemented. Nevertheless, conducting a full case analysis would result in loss of nearly 18% of the sample potentially leading to the group of participants analyzed being unrepresentative of the sample. The vast majority of missing values were attributed to the mediators and demographic confounders as these variables were from the most proximal follow-ups. The second imputation method selected to deal with the high proportion of missing values was multiple imputation using the fully conditional method. Multiple imputation is a superior technique to deal with missing data as it accounts for the uncertainty of missing-data prediction (218). It consists of three phases. First, missing values are filled in numerous times creating multiple data sets; 20 imputations were done in this project to match the proportion of missing cases. These data sets are then analyzed separately and lastly, the estimates are pooled taking into account the uncertainty due to having missing data (218). The fully conditional method was used as it allows a different distribution for each imputed variable; logistic regression was used for binary variables and the predictive mean matching method was used for continuous variables (219). The predictive mean matching method was selected over regression as it imputes random values that are consistent with those observed in the dataset (219). All variables used in the analyses models were used in the multiple imputation model (220). A sensitivity analysis was run using list wise deletion for participants with any missing data to show that the results of the imputed dataset were consistent with those from the complete-case analysis (Appendix F).

Chapter 5

5 Results

The study findings are presented in this chapter beginning with a description of the sample and their families. Next, the results of the attrition and bivariate analyses are presented (Sections 5.2-5.3). The last three sections (5.4-5.6) present the results of each research objective.

5.1 Sample Characteristics

Characteristics of the youth that remained consistent over time (age at diagnosis, sex) and youth self-report measures collected only at 10 years are shown in Table 5.1. Of the 131 youth who participated in the 10-year follow-up, 3 did not report on the outcome of interest (depressive symptoms) and were excluded from the study. Of these youth, 37.2% had depressive symptoms that were clinically significant (CES-D≥16) with a group average CES-D score of 12.6 (SD: 10.2). The youth in our sample ranged in age from 12 to 23 years with the average age being 17.8 (SD: 2.6) years at the 10-year follow-up. These children were diagnosed with epilepsy between the ages of 3 and 12 years, with the group average being 7.5 (SD: 2.5) years. There was a similar proportion of males (48.8%) as there were females (51.2%). At the 10-year follow-up, the majority of youth were living with family (84%) and only 8% were living with a roommate or partner. Almost all the adolescents, except for 2%, were still in school. Of the young adults, 16% were not in school at the 10-year follow-up due to taking a year off, already having completed their post-secondary education, or not planning to continue their educational journey past high school.

Over half (59.7%) the youth had been free of seizures for at least the past five years and very few (11.6%) had experienced a seizure within the past year. Similarly, the majority of the sample were not currently using AEDs (72.1%), with most having discontinued use two or more years ago (65.8%). A small proportion of the youth had never required AEDs to control their seizures (11.8%). The majority of youth were no longer receiving care for their epilepsy (65%) and of those still receiving care, 4% were

receiving epilepsy care from a family doctor, 13% from an adult neurologist, and 8% from a paediatric neurologist.

Characteristics of the families of youth with epilepsy measured at all six data collection points are shown in Table 5.2. The annual family income increased for 53% of families, remained similar for 34%, and decreased for 14% from baseline to the 10-year follow-up. At the 10-year follow-up, nearly half the sample had an annual household income of $100,000 or greater, and very few had an annual household income of less than $40,000 (11.7%). Nearly all of the primary caregivers who participated were the children's biological mothers. At the 10-year follow-up, majority of primary caregivers were working either full or part-time (71%), 9% were not working, 12% were homemakers, and 1% were students. Most primary caregivers had completed some form of post-secondary education (81%), 10% had completed high school and 1% did not. Also at the 10-year follow-up, the majority of primary caregivers were living with a partner (79.1%) with 76% currently married (with 3% of those re-married), 13% divorced, separated or widowed, and 3% never married. Overall, families were functioning well and had an adequate amount of resources and this remained stable over the 10-year period following the child's diagnosis of epilepsy. The average score on the CES-D among primary caregivers was highest at the time of diagnosis, but on average remained stable over time. The prevalence of primary caregivers who had clinically significant depressive symptoms did not fluctuate much over time, ranging from 23% to 28% across time points.

Characteristics of the youth at each of the six data collection points are shown in Table 5.3. In our sample (n=129) the average severity of epilepsy improved from *somewhat severe* at the time of diagnosis to *a little severe* by the six-month follow-up. Following the six-month follow-up, on average, the severity of epilepsy remained stable. From diagnosis to the 2-year follow-up, the severity of epilepsy for about a quarter of the patients remained the same (28%), for approximately half it became less severe (57%), and for 15% it became more severe. The types of seizures children were experiencing were the same as those with which they were initially diagnosed at the 2-year follow-up for almost all the patients (95%). At the 2-year follow-up, 35.7% of children had generalized seizures and 51.2% had partial seizures. The number of children with

cognitive problems nearly tripled from the time of diagnosis to the two-year follow-up, while the increase in the number of children with behavioural problems was minimal. At the 2-year follow-up, 19.4% of children had cognitive problems and 13.2% had behavioural problems.

5.2 Attrition Analysis

A flow chart presenting the number of parents and youth retained at each data collection point can be found in Figures 5.1 and 5.2. A sample of 373 parents of children with newly diagnosed epilepsy were recruited to participate in the study. For the long-term follow-up study at 8 and 10 years post-diagnosis, youth self-report was added. At the 10-year follow-up, 131 (60%) youth self-reported on their health. The results of the attrition analysis comparing youth who participated in the 10-year follow-up of the study with those who did not are presented in Table 5.4. These two groups of youth did not differ in terms of their sex, the age that they were diagnosed with epilepsy, the severity of their epilepsy, or their seizure type. However, those who did not participate in the 10-year follow-up were less likely to have been diagnosed with comorbid cognitive (27% vs. 7%) or behavioural problems (18% vs. 9%) at the time of epilepsy diagnosis. Non-participators were also from families of lower income and fewer family resources, and their primary caregivers were more likely to have depressive symptoms compared to those who participated at the 10-year follow-up. There was no difference between participants and non-participants for the level of family functioning and whether the primary caregiver was living with their partner.

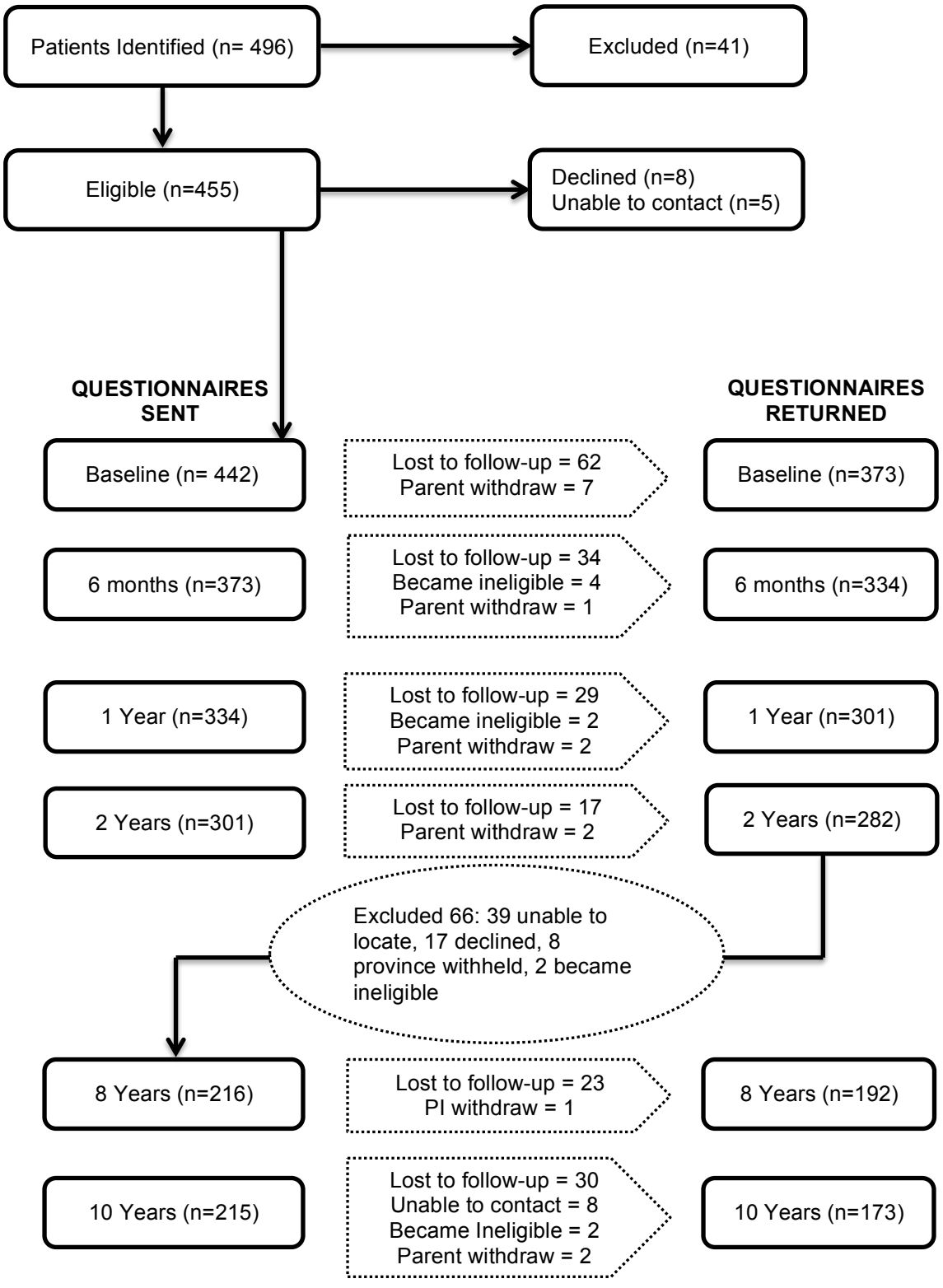

Figure 5.1: HERQULES flow chart of parent sample

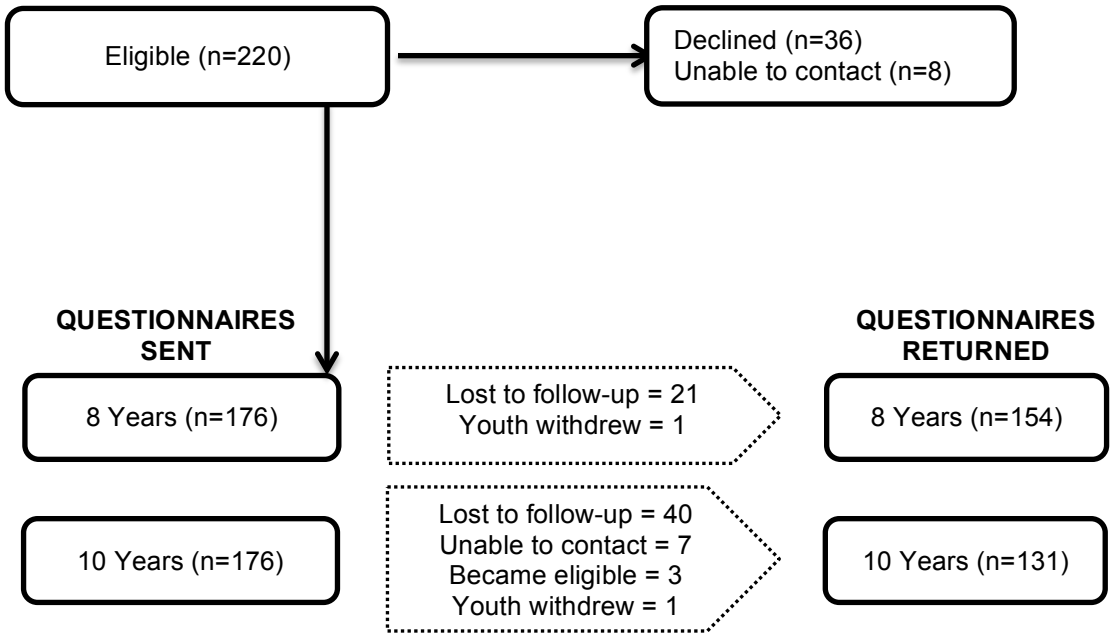

Figure 5.2: HERQULES flow chart of youth sample

5.3 Bivariate Analysis

The results of the bivariate analysis (Table 5.5) suggest that early severity of epilepsy was significantly associated with later depressive symptoms (β= 2.25, 95% CI: 0.63, 3.88). Of the potential confounders, only age at diagnosis was significantly associated with subsequent youth depressive symptoms (β= 0.95, 95% CI: 0.22, 1.68). Of the potential mediators, family functioning (β= -0.60, 95% CI: -1.08, -0.11), family resources (β= -0.20, 95% CI: -0.36, -0.04), five-year seizure freedom (β= 7.65, 95% CI: 4.16, 11.14), and AED use (β= -5.56, 95% CI: -9.55, -1.56) were all significant predictors of youth depressive symptoms. The only potential mediator of the relationship between early severity of epilepsy and subsequent youth depressive symptoms that was not significantly associated with the outcome was parental depressive symptoms (β= 0.06, 95% CI: -0.13, 0.25).

5.4 Objective 1

To determine whether early severity of epilepsy was an independent risk factor for depressive symptoms among youth with epilepsy, a multiple linear regression analysis was conducted adjusting for potential confounders. Severity of epilepsy was measured at the 2-year follow-up and depressive symptoms were measured at the 10-year follow-up. The following clinical and demographic factors were controlled for as potential confounders: seizure type, cognitive problems, behavioural problems, age at diagnosis, sex, family income, and parental living arrangements. The results (Table 5.6) suggest that early severity of epilepsy was significantly associated with depressive symptoms, adjusting for potential confounders, with a parameter estimate of 2.10 (95% CI: 0.42, 3.79 for a 1-unit increase on the GASE scale assessing severity of epilepsy. Thus, the more severe the childhood epilepsy youth had, the more likely they were to have later depressive symptoms.

5.5 Objective 2

5.5.1 Family Functioning

A generalized estimating equations (GEE) model was used to assess the potential mediating effect of family functioning around eight years post-diagnosis on the relationship between early severity of epilepsy and subsequent youth depressive symptoms, adjusting for potential confounders. The potential confounders were the same clinical (seizure type, cognitive problems, behavioural problems, age at diagnosis) and demographic (sex, family income, parental living arrangements) factors that were controlled for in the analysis to address the first objective. The GEE model computed both the direct effect of severity of epilepsy on depressive symptoms, while adjusting for family functioning (M*) and the indirect effect of this relationship (G*severity of epilepsy) (Table 5.7). The total effect of severity of epilepsy assessed in the first objective was 2.10 (95% CI: 0.42, 3.79). Once the potential mediating effects of family functioning were adjusted for, the estimate of the direct effect decreased to 1.86 (95% CI: 0.10, 3.61). The magnitude of the indirect effect (i.e. the difference between the presence of the potential mediator in the model or not) was 0.25, which indicates that family

functioning reduced the effect that severity of epilepsy had on the risk of depressive symptoms by nearly 12%. However, when testing the significance of the indirect effect, the GEE model indicated that family functioning did not mediate the relationship between early severity of epilepsy and subsequent youth depressive symptoms (ab= 0.25, SE: 0.17, 95% CI: -0.08, 0.57).

5.5.2 Family Resources

The potential mediating effect of family resources around eight years post-diagnosis on the relationship between early severity of epilepsy and subsequent youth depressive symptoms, adjusting for potential confounders, was assessed (Table 5.8). The total effect of severity of epilepsy assessed in the first objective was 2.10 (95% CI: 0.42, 3.79 and the estimate of the direct effect when adding family resources (M*) into the model decreased to 1.88 (95% CI: 0.13, 3.63). The magnitude of the indirect effect was 0.22, which indicates that family resources reduced the effect that severity of epilepsy had on the risk of depressive symptoms by 10%. However, when testing the significance of the indirect effect, the GEE model indicated that family resources did not mediate the relationship between early severity of epilepsy and subsequent youth depressive symptoms (ab= 0.22, SE: 0.19, 95% CI: -0.15, 0.59).

5.5.3 Parental Depressive Symptoms

Parental depressive symptoms were not assessed as a potential mediator using a GEE model as the results of the bivariate analysis revealed its lack of association with the outcome of interest. Evidence suggests that a potential mediator must be associated with the outcome to be eligible to mediate the relationship between an exposure and outcome (221–223).

5.6 Objective 3

5.6.1 Five-Year Seizure Freedom

Similar to the second objective, a GEE model was used to assess the potential mediating effect of 5-year seizure freedom by 10 years post-diagnosis on the relationship between

early severity of epilepsy and subsequent youth depressive symptoms, adjusting for potential confounders (Table 5.9). The potential confounders were the same as those in the analyses to address the previous two objectives. The total effect of severity of epilepsy assessed in the first objective was 2.10 (95% CI: 0.42, 3.79 and the estimate of the direct effect when adding 5-year seizure freedom (M*) into the model decreased to -0.89 (95% CI: -1.15, 2.92). The magnitude of the indirect effect was 1.22, which indicates that 5-year seizure freedom decreased the effect that severity of epilepsy had on the risk of depressive symptoms by approximately 58%. When testing the significance of the indirect effect, the GEE model indicated that 5-year seizure freedom mediated the relationship between early severity of epilepsy and subsequent youth depressive symptoms (ab= 1.22, SE: 0.44, 95% CI: 0.35, 2.09). Thus, the effect of early childhood severity of epilepsy was found to be of lesser importance when taking into account the more recent clinical presentation of the disease. Those who had not achieved 5-year seizure freedom were at greater risk of having depressive symptoms as compared to those who had achieved 5 years of seizure freedom by the 10-year follow-up.

5.6.2 Antiepileptic Drug Use

The potential mediating effect of AED use 10 years post-diagnosis on the relationship between early severity of epilepsy and subsequent youth depressive symptoms was assessed (Table 5.10). The total effect of severity of epilepsy assessed in the first objective was 2.10 (95% CI: 0.42, 3.79 and the estimate of the direct effect when adding AED use (M*) into the model decreased to 1.51 (95% CI: -0.51, 3.54). The magnitude of the indirect effect was 0.59, which indicates that AED use decreased the effect that severity of epilepsy had on the risk of depressive symptoms by 28%. However, when testing the significance of the indirect effect, the GEE model indicated AED use to not mediate the relationship between early severity of epilepsy and subsequent youth depressive symptoms (ab= 0.59, SE: 0.44, 95% CI: -0.27, 1.45).

A final note is that without employing multiple imputation (Appendix F), the magnitude and direction of effects from the complete case analysis were similar to the findings presented here.

Table 5.1: Youth characteristics collected at the ten-year follow-up

Youth Characteristics at 10 Years		
Age	mean (SD)	17.8 (2.6)
	range	12-23
Age at Diagnosis	mean (SD)	7.5 (2.4)
	range	3-12
Sex	n (%)	
Male		63 (48.8)
Female		66 (51.2)
Last Seizure	n (%)	
<6 months ago		12 (9.3)
≥6 months ago to <1 year ago		3 (2.3)
≥1 year ago to <2 years ago		7 (5.4)
≥2 years ago to <5 years ago		18 (14.0)
≥5 years ago to <10 years ago		57 (44.2)
10 years ago or more		20 (15.5)
Does not recall		11 (8.5)
Current AED Use	n (%)	
Yes		33 (25.6)
No		93 (72.1)
Last AED Used	n (%)	
<6 months ago		2 (2.2)
≥6 months ago to <1 year ago		0 (0)
≥1 year ago to <2 years ago		2 (2.2)
≥2 years ago		61 (65.6)
Has never taken medication for seizures		11 (11.8)
Does not recall		14 (15.1)

*For the 'last seizure' variable this table does not include imputed values from the parent-report for children who reported 'do not recall'.

Table 5.2: Family characteristics at each of the six data collection points

Family Characteristics	Baseline	6 Months	1 Year	2 Years	8 Years	10 Years
Income n(%)						
<$20,000	6 (4.7)	9 (7.0)	6 (6.7)	6 (4.7)	4 (3.1)	2 (1.6)
$20,000-$39,999	12 (9.3)	14 (10.9)	17 (13.2)	14 (10.9)	11 (8.6)	13 (10.1)
$40,000-$59,999	24 (18.6)	17 (13.2)	16 (12.4)	21 (16.3)	11 (8.6)	9 (7.0)
$60,000-$79,999	22 (17.1)	18 (14.0)	17 (13.2)	23 (17.8)	15 (11.6)	15 (11.6)
$80,000-$99,999	22 (17.1)	22 (17.1)	24 (18.6)	14 (10.9)	17 (13.2)	16 (12.4)
≥$100,000	38 (29.5)	42 (32.6)	43 (33.3)	45 (34.9)	59 (45.7)	61 (47.3)
Does not know	1 (0.8)	3 (2.3)	4 (3.1)	1 (0.8)	6 (4.7)	2 (1.6)
Parental Living Arrangements n(%)						
Yes	116 (89.9)	112 (86.8)	113 (87.6)	114 (88.4)	106 (82.2)	102 (79.1)
No	13 (10.1)	16 (12.4)	16 (12.4)	15 (11.6)	18 (14.0)	17 (13.2)
Family Functioning	14.3 (3.9)	14.4 (3.7)	14.2 (4.0)	14.2 (3.8)	14.2 (3.7)	14.6 (4.0)
n=	129	128	129	128	124	119
Family Resources	52.8 (10.7)	52.4 (11.5)	52.2 (10.8)	50.9 (11.5)	51.2 (11.3)	51.7 (11.9)
n=	129	127	128	128	124	119
Parental Depressive Symptoms n(%)	12.3 (9.5)	10.0 (8.6)	11.3 (8.4)	11.5 (9.6)	11.2 (9.4)	10.0 (9.0)
CES-D score ≥16	36 (28.1)	29 (22.8)	35 (27.3)	33 (25.6)	34 (27.4)	27 (22.7)
CES-D score <16	92 (71.9)	98 (77.2)	93 (72.7)	96 (74.4)	90 (72.6)	92 (77.3)

*Mean and standard deviation provided, unless otherwise stated.
*Family Functioning (APGAR) scores range from 1 to 20.
*Family Resources (FIRM) scores range from 16 to 72.
*Parental Depressive Symptoms (CES-D) scores range from 0 to 40.

Table 5.3: Youth characteristics at each of the six data collection points

Characteristics	Baseline	6 Months	1 Year	2 Years	8 Years	10 Years
Severity of Epilepsy						
mean (SD)	2.5 (1.1)	1.9 (1.1)	1.9 (1.1)	1.7 (1.1)	1.8 (1.1)	1.8 (1.2)
n=	125	120	118	117	30	32
Seizure Type						
Generalized	53 (41.1)	54 (41.9)	51(39.5)	46 (35.7)	18 (14.0)	20 (15.5)
Partial	75 (58.1)	69 (53.5)	68 (52.7)	66 (51.2)	9 (7.0)	11 (8.5)
Undetermined	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	1 (0.8)
Cognitive Problems						
Yes	9 (7.0)	10 (7.8)	21 (16.3)	25 (19.4)	9 (7.0)	10 (7.8)
No	120 (93.0)	113 (87.6)	96 (74.4)	92 (71.3)	20 (15.5)	22 (17.1)
Behavioural Problems						
Yes	12 (9.3)	18 (14.0)	15 (11.6)	17 (13.2)	8 (6.2)	8 (6.2)
No	116 (89.9)	104 (80.6)	103 (79.8)	101 (78.3)	22 (17.1)	24 (18.6)

*Frequency (%) reported, unless otherwise stated.

Table 5.4: Sensitivity analysis comparing baseline characteristics of youth retained for the ten-year follow-up and those who did not participate

Variable	Did Not Participate (n=242)	Completed Follow-Up (n=131)	p-value
Sex			0.23
Male	132 (55%)	63 (48%)	
Female	110 (45%)	68 (52%)	
Age at Diagnosis (*mean)*	7.27	7.53	0.30
Seizure Type			0.74
Generalized	89 (37%)	54 (41%)	
Partial	145 (60%)	75 (57%)	
Undetermined	5 (2%)	2 (2%)	
Severity of Epilepsy (*mean)*	2.68	2.45	0.07
Behavioural Problems			0.02
Yes	44 (18%)	12 (9%)	
No	195 (81%)	118 (90%)	
Cognitive Problems			<0.0001
Yes	65 (27%)	9 (7%)	
No	173 (71%)	122 (93%)	
Household Income			0.008
<$50,000	89 (37%)	32 (24%)	
$50,000-$99,999	93 (38%)	56 (43%)	
>$100,000	42 (17%)	38 (29%)	
Parental Living Arrangements			0.15
Living with spouse/partner	205 (85%)	118 (90%)	
Not living with spouse/partner	37 (15%)	13 (10%)	
Family Functioning (*mean)*	13.68	14.32	0.12
Family Resources (*mean)*	48.68	52.62	0.001
Parental Depressive Symptoms (*mean)*	15.35	12.33	0.007

*Reported as frequencies, unless otherwise stated.
*The p-value is from a chi-square or fisher's exact test for categorical variables and t-test for continuous variables.

Table 5.5: Bivariate analysis with exposure, potential clinical and demographic confounders, and potential family and clinical mediators

Variable	Co-efficient (SE)	95% Confidence Interval
Severity of Epilepsy	2.25 (0.82)**	0.63, 3.88
Sex *(ref=male)*	0.84 (1.80)	-2.72, 4.40
Age at Diagnosis	0.95 (0.37)*	0.22, 1.68
Seizure Type *(ref=generalized)*	1.67 (1.83)	-1.94, 5.29
Cognitive Problems *(ref=yes)*	-1.86 (2.31)	-6.44, 2.71
Behavioural Problems *(ref=yes)*	-2.64 (2.67)	-7.93, 2.65
Family Income *(ref =<50,000)*	-0.90 (0.86)	-2.60, 0.80
Parental Living Arrangements *(ref=yes)*	2.48 (2.56)	-2.60, 7.56
Family Functioning	-0.60 (0.24)*	-1.08, -0.11
Family Resources	-0.20 (0.08)*	-0.36, -0.04
Parental Depressive Symptoms	0.06 (0.10)	-0.13, 0.25
Five-Year Seizure Freedom *(ref=yes)*	7.65 (1.76)***	4.16, 11.14
AED use *(ref=yes)*	-5.56 (2.02)**	-9.55, -1.56

*p<0.02, **p<0.01, ***p<0.0001

Table 5.6: Multivariate regression analysis assessing the relationship between severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders with multiple imputation (n=129)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	2.61 (8.76)	-14.56, 19.78
Severity of Epilepsy	2.10 (0.86)*	0.42, 3.79
Sex	0.18 (1.82)	-3.38, 3.74
Age at Diagnosis	0.97 (0.38)*	0.23, 1.71
Seizure Type	2.25 (1.81)	-1.29, 5.79
Cognitive Problems	0.69 (2.43)	-4.07, 5.45
Behavioural Problems	-3.59 (2.80)	-9.07, 1.89
Family Income	0.08 (1.00)	-1.88, 2.04
Parental Living Arrangements	0.54 (2.82)	-4.99, 6.07

Note: The mean R^2 across imputations was 12.5% (range: 12.1% to 13.0%).
*p<0.02

Table 5.7: GEE model assessing family functioning as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders with multiple imputation (n=129)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	10.74 (9.23)	-7.35, 28.82
Severity of Epilepsy	1.86 (0.90)*	0.10, 3.61
Sex	-0.79 (1.78)	-4.29, 2.70
Age at Diagnosis	0.98 (0.35)**	0.30, 1.67
Seizure Type	1.92 (1.67)	-1.34, 5.19
Cognitive Problems	0.74 (2.34)	-3.85, 5.32
Behavioural Problems	-3.22 (3.11)	-9.30, 2.87
Family Income	0.36 (0.98)	-1.56, 2.28
Parental Living Arrangements	-0.15 (2.76)	-5.56, 5.27
G	-8.13 (4.65)	-17.24, 0.98
M*	-0.46 (0.26)	-0.97, 0.04
G*Severity of Epilepsy	0.25 (0.17)	-0.08, 0.57
G*Sex	0.97 (0.56)	-0.13, 2.07
G*Age at Diagnosis	-0.01 (0.05)	-0.12, 0.09
G*Seizure Type	0.33 (0.33)	-0.32, 0.97
G*Cognitive Problems	-0.05 (0.40)	-0.82, 0.73
G*Behavioural Problems	-0.38 (0.50)	-1.35, 0.60
G*Family Income	-0.28 (0.21)	-0.68, 0.13
G*Parental Living Arrangements	0.69 (0.63)	-0.54, 1.91

*p<0.05, **p<0.01

Table 5.8: GEE model assessing family resources as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders with multiple imputation (n=129)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	10.00 (10.04)	-9.68, 29.67
Severity of Epilepsy	1.88 (0.89)*	0.13, 3.63
Sex	0.08 (1.73)	-3.31, 3.46
Age at Diagnosis	0.88 (0.36)**	0.18, 1.59
Seizure Type	2.03 (1.70)	-1.29, 5.36
Cognitive Problems	1.09 (2.38)	-3.57, 5.75
Behavioural Problems	-3.59 (3.02)	-9.52, 2.33
Family Income	0.46 (1.02)	-1.55, 2.46
Parental Living Arrangements	-0.44 (2.80)	-5.94, 5.06
G	-7.39 (5.53)	-18.23, 3.46
M*	-0.13 (0.09)	-0.31, 0.06
G*Severity of Epilepsy	0.22 (0.19)	-0.15, 0.59
G*Sex	0.10 (0.22)	-0.33, 0.54
G*Age at Diagnosis	0.09 (0.07)	-0.06, 0.23
G*Seizure Type	0.22 (0.28)	-0.34, 0.77
G*Cognitive Problems	-0.40 (0.48)	-1.33, 0.53
G*Behavioural Problems	0.00 (0.30)	-0.58, 0.58
G*Family Income	-0.37 (0.30)	-0.97, 0.22
G*Parental Living Arrangements	0.98 (0.82)	-0.62, 2.58

*p<0.05, **p<0.02

Table 5.9: GEE model assessing five-year seizure freedom as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders with multiple imputation (n=129)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	-5.21 (7.99)	-20.87, 10.45
Severity of Epilepsy	0.89 (1.04)	-1.15, 2.92
Sex	0.45 (1.73)	-2.94, 3.83
Age at Diagnosis	0.90 (0.34)**	0.24, 1.56
Seizure Type	2.21 (1.68)	-1.07, 5.50
Cognitive Problems	-0.32 (2.47)	-5.16, 4.53
Behavioural Problems	-1.66 (3.04)	-7.62, 4.30
Family Income	0.17 (0.94)	-1.67, 2.01
Parental Living Arrangements	0.55 (2.50)	-4.35, 5.46
G	7.82 (3.46)*	1.03, 14.61
M*	5.91 (2.09)***	1.82, 10.01
G*Severity of Epilepsy	1.22 (0.44)**	0.35, 2.09
G*Sex	-0.27 (0.48)	-1.20, 0.67
G*Age at Diagnosis	0.07 (0.11)	-0.13, 0.28
G*Seizure Type	0.04 (0.46)	-0.86, 0.94
G*Cognitive Problems	1.01 (0.69)	-0.35, 2.36
G*Behavioural Problems	-1.93 (1.04)	-3.97, 0.10
G*Family Income	-0.09 (0.25)	-0.58, 0.41
G*Parental Living Arrangements	-0.01 (0.74)	-1.47, 1.45

*P>0.05, **p<0.01, ***p<0.005

Table 5.10: GEE model assessing AED use as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders with multiple imputation (n=129)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	10.14 (10.93)	-11.30, 31.57
Severity of Epilepsy	1.51 (1.03)	-0.51, 3.54
Sex	-0.01 (1.76)	-3.45, 3.44
Age at Diagnosis	0.87 (0.36)*	0.17, 1.57
Seizure Type	2.67 (1.63)	-0.53, 5.87
Cognitive Problems	0.02 (2.44)	-4.77, 4.81
Behavioural Problems	-2.76 (2.97)	-8.57, 3.06
Family Income	-0.08 (0.96)	-1.97, 1.82
Parental Living Arrangements	0.26 (2.74)	-5.11, 5.62
G	-7.53 (5.59)	-18.48, 3.43
M*	-3.33 (2.43)	-8.10, 1.44
G*Severity of Epilepsy	0.59 (0.44)	-0.27, 1.45
G*Sex	0.19 (0.29)	-0.38, 0.75
G*Age at Diagnosis	0.10 (0.09)	-0.08, 0.28
G*Seizure Type	-0.42 (0.38)	-1.18, 0.33
G*Cognitive Problems	0.67 (0.59)	-0.49, 1.83
G*Behavioural Problems	-0.84 (0.76)	-2.33, 0.66
G*Family Income	0.16 (0.18)	-0.20, 0.52
G*Parental Living Arrangements	0.28 (0.40)	-0.50, 1.07

*p<0.02

Chapter 6

6 Discussion

This chapter begins with a summary and interpretation of the study results (Section 6.1). Next, the strengths and limitations of our study will be presented (Sections 6.2-6.3) followed by recommendations for future research and the implications of our study (Sections 6.4-6.5).

6.1 Summary of Results

This thesis aimed to assess the association between early severity of epilepsy and subsequent depressive symptoms in youth diagnosed with epilepsy during their childhood. With the stress process model as the guiding conceptual framework, family factors were examined as potential mediators of this relationship. Given the lengthy time period between the exposure and outcome, current clinical characteristics were also examined as potential mediators of the relationship between severity of epilepsy and youth depressive symptoms. To our knowledge, our study is the first to assess the nature of the relationship between early severity of epilepsy in childhood and depressive symptoms during adolescence and young adulthood.

6.1.1 Relationship Between Severity of Epilepsy and Depressive Symptoms

The first objective of this thesis was to assess the association between severity of epilepsy early in the course of the disease and subsequent depressive symptoms. Childhood epilepsy was presumed to have a lasting impression on children's psychiatric health during their adolescent and young adulthood years due to its impact on their psychosocial development. Indeed, this study found early severity of epilepsy to be significantly associated with subsequent youth depressive symptoms. The more severe childhood epilepsy youth had, the greater their risk was for depressive symptoms as adolescents and young adults. This finding is of clinical importance for neurologists as they routinely assess patients' severity of epilepsy. In the early course of the disease, neurologists may be able to predict which children are at higher risk of acquiring depression later in their

life and as such may educate parents whose child has a history of severe epilepsy on how to effectively monitor them for symptoms of depression. They may also recommend parents to promote positive mental health, provide a nurturing social environment, and may refer patients to mental health professionals on a case-by-case basis.

Although no other study has examined early disease severity in childhood epilepsy as a risk factor for future psychiatric illnesses, cross-sectional studies have found an association between severity of seizures or epilepsy and psychiatric disorders (78–81). Austin et al. (1996) examined illness severity, a measure based on seizure type, frequency of seizures, and the number of AEDS/presence of side effects, as a predictor of mother and teacher reported internalizing problems, which include behaviours such as withdrawal, depression, and somatic complaints. They found that youth in the highest severity of epilepsy group had significantly more internalizing problems, as reported by both mothers and teachers using the Child Behaviour Checklist, compared to youth in the lowest severity group. Using the same sample of youth with epilepsy, Haber et al. (2003) examined disease severity as a risk factor of both self concept, measured using the Children's Self-Concept Scale and depression, measured using the CDI. They had similar findings, where severity of epilepsy was highly correlated with self-concept, and marginally (yet not significantly) correlated with youth depression symptoms. Their sample differed from ours in two ways: the mean age of diagnosis for their sample was slightly younger (4.9 years vs. 7.5 years) and patients who were not receiving treatment for a year prior to study entry were excluded which was not a requirement for our study sample. As such, they excluded patients with less severe epilepsy not requiring treatment, potentially decreasing the range of disease severity in their sample. Our studies also differed in the follow-up times used for assessing severity of epilepsy and depressive symptoms, as they assessed both concurrently four years after study entry; consequently, it is unknown when the onset of depression occurred relative to epilepsy diagnosis. We assessed severity of epilepsy 2 years after diagnosis and depressive symptoms 10 years after diagnosis, allowing a temporal order between exposure and outcome. As severity of epilepsy changes over time, it is likely to influence the risk of depressive symptoms differently depending on when it is measured and when depressive symptoms are measured. Similarly, Chew et al. (2017) found higher severity of epilepsy to be

associated with poorer self-esteem using the same measure for severity. The final study by Turky at el. (2008) examined severity of seizures as a risk factor for psychiatric disorders; despite their small sample size (n=56), they had findings consistent with our study. Their results showed that increased severity of seizures and epilepsy, measured using the Liverpool Seizure Severity Scale, was associated with the risk of parent-reported depression and emotional problems in youth ages 5 to 17 with epilepsy.

Near the time of seizure-onset, a highly predictive characteristic of severity of epilepsy, frequency of seizures, has been found to be associated with depression in adolescents (82,83). In the first study, children and adolescents ages 9 to 18 who had daily seizures in the early stages of their epilepsy were found to be at a higher risk of depression and anxiety as compared to those who only had one seizure or were seizure free (83). This study had a very small sample of 35 patients with an onset of epilepsy ranging from 1 to 15.5 years. Depression was assessed using the CDI and anxiety was assessed using the State Trait Anxiety Inventory. The second study with a larger sample (n=140) of adolescents ages 10 to 18 years found more frequent weekly or daily seizures at onset were associated with the risk of depression but not anxiety, measured using the HADS (82). A notable distinction between these two studies is that the average disease duration of the first study was larger at 5.6 (SD:3.9) years as compared to the latter study with an average disease duration of 3.6 (SD:2.2) years for children and 4.8 (SD:3.4) years for adolescents. Accordingly, patients in the last study may not have had anxiety due to their longer duration of disease providing them with a longer window of time to adapt. No other studies were found that examined characteristics of early childhood severity of epilepsy as risk factors for later depressive disorders, as such there are no studies with opposing findings.

6.1.2 Family Factors as Mediators

The second objective examined the potential mediating effects of family functioning, family resources, and parental depressive symptoms in the relationship between early severity of epilepsy and subsequent youth depressive symptoms. The rationale behind this objective was that in previous studies these family factors had been found to be associated with both the exposure and outcome. Clinical aspects of epilepsy, including a

longer disease duration and higher frequency of seizures, have been found to be associated with poorer family functioning and consequently, poor family functioning has been found to be associated with depression in children with epilepsy (80,121,140,149,154,168). Level of family resources were previously found to be associated with severity of epilepsy and the risk of depression and internalizing behavior problems in children with epilepsy (81,86,140,156). Parental depressive symptoms have been shown to be associated with both severity of epilepsy and youth behavioural problems including depressive disorders (172,185). Furthermore, these family factors were found to be mediators of other similar relationships. A study of children with chronic illnesses, including epilepsy, found the relationship between having a chronic childhood illness and symptoms of anxiety and depression to be mediated by changes in both family dysfunction and maternal symptoms of depression over time (224). Among children with epilepsy, family mastery, an aspect of family resources, was found to mediate the relationship between severity of epilepsy and self-esteem (81). To the best of our knowledge, this is the first study to examine family functioning, family resources, and parental depressive symptoms as mediators of the relationship between severity of epilepsy and depressive symptoms.

Contrary to expectation, the results of our study suggest that the relationship between early childhood severity of epilepsy and subsequent youth depressive symptoms was not mediated by family functioning, family resources, or parental depressive symptoms. There are a number of factors one might consider as potentially explaining these findings. First, the majority of the sample had very mild epilepsy and thus their epilepsy may not have created as much disruption in the family environment as more severe epilepsy might have. This is supported by a previous study where families with children who had uncontrolled epilepsy were at a higher risk of having a poor quality of life (150). The results of our study also showed that most families were functioning well overall and had an adequate amount of resources. Hence, there was minimal variability in the sample, with most of the children living in a thriving family environment. As such, we may have been underpowered to detect a mediating effect for the family factors due to this lack of variability. The attrition analysis also revealed that families with lower household incomes, fewer resources, and parental depressive symptoms were less likely

to participate in the 10-year follow-up of this study. It is possible that if we had more disadvantaged families participate, the family factors would have presented as mediators.

Second, there is potential for age-effects as the role of family factors, the severity of epilepsy, and depressive symptoms may differ between adolescents and young adults. Young adults may have greater autonomy and be less likely to be influenced by their family environment, relative to adolescents. Emerging adulthood (usually ages 18 to 25) is a time where many individuals move out of their homes to either attend post-secondary institutions, begin employment, or to live with their romantic partner whereas others continue to reside with their parents but begin to make independent life decisions (225). Differences in the prognosis of epilepsy based on age of diagnosis may exist as a long-term prospective study found children diagnosed between the ages of 5 and 9 to be at the highest risk of having intractable epilepsy (226). Lastly, there may also be age-related differences in the prevalence of depression (227). To explore the potential for age effects in our study, a post-hoc analysis was conducted performing a stratified analysis separating adolescents (ages 12 to 17 years) from young adults (ages 18 to 24 years). The results of the relationship between early severity of epilepsy and youth depressive symptoms was no longer significant for either of the age groups. Subsequently, given no total effect between severity of epilepsy and depressive symptoms, the family factors were not mediators of this relationship. This may have been attributed to the small sample sizes as there were only 62 adolescents and 67 young adults. Alternatively, age effects may truly not exist as the prevalence of young adults in Canada co-residing with their parents is increasing over time (228). Youth with chronic illnesses are especially likely to be dependent on their parents longer (229) and as such, are likely affected by their family environment similar to their adolescent counterparts. This was the case in our study where only 8% of our sample was not residing with a family member at the 10-year follow-up.

Third, the effect of family factors may have differed depending on the sex of the primary caregiver who reported them. Psychiatric illness among mothers, but not fathers, has been found to increase the risk of psychiatric illnesses in children with epilepsy (136). Moreover, sex differences exist in the prevalence of depression in adults, with women more commonly presenting with depression (230,231). There may be dissimilarities in

how women and men react to their child's disease severity as mothers and fathers have been found to have differing attitudes towards their child's epilepsy (80). These differences in parenting attitudes may be attributed to one parent being the primary caregiver and having different experiences with the child by communicating with and watching over the child more often than the other parent. It is difficult to assess whether these sex-based differences exist when examining only primary caregivers due to the small number of male primary caregivers in Canada. To achieve a homogenous sample of primary caregivers and reduce the risk of sex-based differences, a post-hoc analysis was done removing the five participants whose primary caregiver was their father. The results of the analyses remained consistent for all objectives as those presented in this thesis. This may be attributed to the negligible influence having fathers in the sample may have had due to their small sample size. The small proportion of primary caregivers being fathers is consistent with the gender of primary caregivers of children with health problems in Canada where the majority are mothers (232). Additionally, although discrepancies between mother's and father's ratings of family functioning and family resources have been found (80) these discrepancies may be minimal when the fathers included are the primary caregivers and have similar experiences to the primary caregiving mothers.

Finally, it is possible that the potential family mediators act in a causal chain to mediate the relationship between severity of epilepsy and depressive symptoms. Following the social interactional and ecological theoretical framework, family factors have been grouped into four clusters based on their degree of proximity to the child's everyday experience: proximal, distal, contextual, and global (family socio-economic status) (233). Rodenburg et al. (2006) suggested that proximal family factors (the quality of the parent-child relationship and parenting) are the strongest predictors of child psychopathology and thus, mediate the effects of contextual (the quality of other family relationships) and distal factors (parental characteristics). They found the effects of both parental depression and family functioning on the risk of child internalizing problems to be mediated by parental rejection. In our study, parental depressive symptoms would qualify as a distal family factor and family functioning and family resources would be contextual factors. Hence, it is plausible that parental depressive symptoms may affect

family functioning or family resources, which in turn, may lead to youth depressive symptoms. This has been shown in a study where the effect of family functioning on the outcome of youth internalizing problems was mediated by parental depressive symptoms (234). Still, these relationships are complex with another study finding that family functioning mediated the relationship between parental depressive symptoms and child emotional well-being and family resources mediated the effect of family functioning in a multiple mediation pathway (170). Differences in how family factors interact may be attributed to the youth's age; cultural differences in parenting styles, as some cultures exercise stricter parenting than others; or the severity of epilepsy with more severe epilepsies having a greater impact on the family.

Given the increased recognition of the value that family-centered care (FCC) has in improving both family and child outcomes, there is a need to further examine the role of family environment in childhood epilepsy to identify suitable targets for interventions (235). According to the Maternal and Child Health Bureau, the following activities characterize FCC: acknowledging the family as the constant in a child's life, building on family strengths, supporting the child in participating, honoring diversity, recognizing the importance of community-based services, promoting an individual and developmental approach, encouraging family-to family/peer support, developing family-centered policies and practices, and celebrating success. Family factors not explored in our study that may also be targeted within the FCC framework include increasing parents' confidence in managing their child's epilepsy and teaching parents how to provide emotional support for their child (236). Both these factors may be affected by the severity of epilepsy and have been previously found to decrease child behaviour problems over time qualifying them as potential mediators for future studies to examine (156).

6.1.3 Current Clinical Factors as Mediators

The third and final objective examined the potential mediating effects of five years of seizure freedom and AED use, a decade post-diagnosis, for the relationship between early severity of epilepsy and depressive symptoms. The rationale behind this objective was to determine whether early severity of epilepsy is a risk factor for future depressive symptoms or whether its effect is based on it being a predictor of future severity of

epilepsy. Past studies have shown that early disease severity may be a predictor for whether a child will ever reach remission (77,237). Children with controlled epilepsy in the early stages are also the ones who successfully discontinue AED use (74–76).

The results of our study found that five-year seizure freedom mediates the relationship between early severity of epilepsy and subsequent depressive symptoms, reducing the effect of severity of epilepsy by 58%. This finding indicates that most of the effect of early disease severity is through gaining five-year seizure freedom which in turn, is associated with the risk of depressive symptoms. Those who have been free of seizures for the past five years a decade post-diagnosis are at lower risk of having depressive symptoms compared to those who have experienced a seizure in the past five years. This may be due to the fact that youth who have been free of seizures for this long are no longer emotionally or socially affected by their epilepsy and thus are not at as high of a risk of depressive symptoms, as compared to youth with active epilepsy. This is supported by other studies, as one found PWE who have been in remission for greater than five years to have less subjective handicap on all aspects of their daily life including physical, social, emotional, and occupational (114). The authors suggest that this finding may be attributed to a situation whereby the increasing time of remission increases patients' confidence that their epilepsy is resolved for good. Similarly, in another study, adults who experienced none or very few seizures in the past year reported lower illness intrusiveness in domains including relationship and personal development, intimacy, and instrumental life compared to those who had frequent seizures (113).

Although five-year seizure freedom has not been examined as a mediator, the results of one study are consistent with our findings where not being free of seizures for the past five years was associated with the risk of reporting internalizing problems (mainly depression and anxiety) (111). This study had a larger sample size (n=277) with children diagnosed up to 11 years of age, and as such they had a younger age range at their 9-year follow-up (8 to 17 years). In their sample, 64% of youth were free of seizures by the 9-year follow-up and 31% were using AEDs, these proportions are similar to our sample where 65% of youth had 5-year seizure freedom and 26% were using AEDs at the 10-year follow-up. Discordantly, in the same cohort of children, five-years of seizure freedom was not associated with children's HRQoL, but psychiatric disorders were

associated with HRQoL (110). One reason presented by the authors for this lack of association was that they used a generic instrument to measure HRQoL that may not have been sensitive to changes in epilepsy. A multi-step mediation pathway may also exist where five-year seizure freedom predicts psychiatric disorders which in turn, predict HRQoL. A population-based Canadian study of non-institutionalized PWE (N=713) over the age of 15 (Mean: 45.4 years) with 'active epilepsy', defined as either using an AED or experiencing a seizure within the past five years, found five-year seizure freedom to be associated with decreased odds of depression (112). Another study had consistent findings where significantly fewer adults with one-year seizure freedom (4%) had depression compared to those with active epilepsy (17%) (115). Although this study was cross-sectional, it had a large sample size (n=1069) and measured depression using a diagnostic screening tool (HADS).

AED use was the second potential clinical mediator examined and the results found that it was not a mediator of the relationship between early severity of epilepsy and depressive symptoms. Although AED use was not a mediator, it did reduce the effect of early severity of epilepsy rendering it a non-significant risk factor for subsequent depressive symptoms. This may be due to the fact that there was a large but not full overlap between the variables of AED use and five-year seizure freedom. The majority but not all of the youth who were no longer using AEDs were the ones who have been free of seizures for the past five years. A explanation for the non-significant mediating effect is that AEDs have been shown to have psychotropic effects with some reducing and others increasing symptoms of depression (238). Unfortunately, we were unable to account for AED types due to lack of information on which AEDs youth were prescribed. This information likely would not have been that valuable due to the small sample of youth who were using AEDs and the availability of several AEDs in Canada, with some youth using various combinations. There may have also been a difference in the risk of depression for youth on polytherapy treatment compared to those only using one AED but, due to the lack of information and the small sample size, this could not be explored.

The findings of this study indicate that reaching five-years of seizure freedom after a few years of having active epilepsy should be of paramount importance for clinicians. Whether there is a difference between those who are in remission with

treatment and those who are in remission without treatment must be explored further due to the small number of youth in remission with treatment in our sample. Findings from a study of adults with childhood-onset epilepsy followed for over 30 years indicated that those in 5-year seizure remission without treatment were influenced less by their epilepsy as compared to both those not in remission and those in remission with treatment (239). This is consistent with the Antiepileptic Drug Withdrawal Study that included patients over the age of 15 who were free of seizures for the past two years randomized to either slow or no discontinuation of AEDs (240). They found individuals in remission with treatment had greater feelings of stigma, felt that epilepsy restricted their social activities, and believed it affected their work and employment opportunities. These findings may be attributed to the successful discontinuation of AEDs lowering stigma associated with having active epilepsy.

6.2 Strengths

The longitudinal prospective nature of this study allowed temporality between the exposure, mediators, and outcome; a practice ideal for mediation analysis. It was one of the first long-term follow-up studies that allowed for the examination of the occurrence of a psychiatric disorder nearly a decade after the diagnosis of epilepsy in children. This study included only new-onset cases of epilepsy so was an incident sample with a sample size comparable to that of other studies. Data were collected at multiple time points making recall bias highly unlikely. It is also one of only a few long-term studies to include family factors as reported by the most knowledgeable person in the household, the primary caregiver. The potential family mediators and the outcome of interest, youth depressive symptoms, were all measured using validated tools. The exposure of interest, severity of epilepsy, was physician reported using a validated measurement tool making it a standardized measure of disease severity for all participants. The cohort in this study was representative of the general population of youth with epilepsy as the majority of cases were not severe. Lastly, this study provided an opportunity to examine the clinical presentation of the disease in the early stages and its relationship to the presence of seizures in the future.

6.3 Limitations

This study was limited by the fact that depression in the early stages of epilepsy was not measured so causality between severity of epilepsy and depressive symptoms cannot be inferred. Measures for depressive symptoms would not have been feasible to implement given the young age of the sample at the time of diagnosis and the self-administered format for questionnaire completion. According to the parents' reports on their child's psychiatric disorder history, diagnosis of depression, if applicable, occurred after the diagnosis of epilepsy for our entire sample. A screening tool was used to identify who may be at risk for depression rather than a diagnostic tool hence we cannot make inferences regarding who has a depressive disorder and who does not.

Within the stress process model, we have specified the direction of the relationships between variables, it is however possible that the outcome may have affected the mediators. If youth depressive symptoms were chronic and were present for over two years, they may have affected family functioning, family resources, and parental depressive symptoms. Youth depressive symptoms may have also influenced whether youth achieved five-year seizure-freedom if they required AEDs to control their seizures and their psychiatric health affected their compliance to their medication.

Although we had a range in severity of epilepsy, we did not have many youth who had very severe epilepsy and no one in our sample required surgery to control their seizures. This means we cannot claim our findings are generalizable to youth with intractable epilepsy. The loss of families who had lower household incomes, fewer family resources, and were more likely to have parental depressive symptoms, produced a loss in the variability of family environment. With the loss of families who would be most at risk for negative outcomes, we were less likely to find significant effects for family factors. Accordingly, our findings may not be generalizable to low socio-economic status areas or disadvantaged populations. Our sample size, although one of the largest for a long-term follow-up study in childhood epilepsy, may have been underpowered to detect significant results in some of our analyses.

6.4 Recommendations for Future Research

Future studies are warranted to explore the complexity of the relationship between epilepsy-related clinical factors, family environment, and youth depressive disorders given the importance of family in childhood epilepsy. These studies may examine different family factors, the roles of family factors in multiple mediator models and the potential moderating effects of family factors. Following family environment as children age, peer social support becomes important and may be a factor to examine as a potential mediator between severity of epilepsy and mental health outcomes. In a previous study, it was found to mediate the relationship between disease severity and family mastery (241). Studies with larger samples may examine the effects of age by stratifying by adolescent and adult ages given relatively different stressors between these age groups. Future studies should repeat a similar study with different psychiatric disorders as they are very common in youth with epilepsy such as anxiety or suicide. Future studies should also repeat a similar study in a more severe population of youth with epilepsy or those in disadvantaged areas.

6.5 Implications and Conclusions

The findings from this study suggest that early severity of epilepsy in childhood may be associated with depressive symptoms years later during adolescence and young adulthood. Health care professionals may consider educating parents on the high prevalence of depression in youth with epilepsy and offer resources on how depressive symptoms may present to aid parents in recognizing depression if it occurs. Physicians may also consider routinely screening for depression during examinations. A screening tool called the Neurological Disorders Depression Inventory for Epilepsy is a validated epilepsy population specific tool that can rapidly detect depression in clinics and is not resource intensive (37). Although our study did not find family factors to play mediating roles in the relationship between severity of epilepsy and depressive symptoms, this does not imply that they are not important. More research is required to uncover the roles of various family factors, their interrelations, and the usefulness of FCC in families of children with epilepsy. The finding that the influence of early severity of epilepsy is

mediated by seizure freedom for the past five years a decade after diagnosis of epilepsy indicates that children with severe childhood epilepsy are mostly at a high risk of depressive symptoms if they do not eventually gain control of their seizures. Having severe childhood epilepsy does not necessarily condemn children to have unfavourable psychiatric health in their adult years given there are opportunities to improve disease severity with surgery and other interventions if it does not resolve with AEDs.

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APPENDIX A: PHYSICIAN FORM

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

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

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

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

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

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

   3)_____ 4)_____

4. Epilepsy syndrome: _____

5. Convulsive status epilepticus:
   - ☐ No
   - ☐ Yes

6. Exclusive nocturnal seizures:
   - ☐ No
   - ☐ Yes

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

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

9. Number of AEDs <u>currently</u>: _____

10. Number of AEDs <u>total:</u> _____

11. Is this patient of school age?
   - ☐ No
   - ☐ Yes → Grade: ___ ☐ regular class ☐ regular class with resource ☐ special class

12. Does the patient have behavioural problems?

☐ No (normal)

☐ Yes → Please check one**:** ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

13. Does the patient have cognitive problems?

☐ No (normal)

☐ Yes → Please check one: ☐ borderline ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

14. Does this patient have motor problems?

☐ No

☐ Yes → Please check one: ☐ mild ☐ moderate ☐ severe

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

_____

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

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

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

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

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

APPENDIX B: YOUTH SELF-REPORT MEASUREMENT TOOLS

Center for Epidemiological Studies Depression Scale (CES-D)

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.

	During the Past Week:			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
a) I was bothered by things that usually don't bother me.	☐	☐	☐	☐
b) I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
c) I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
d) I felt that I was just as good as other people.	☐	☐	☐	☐
e) I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
f) I felt depressed.	☐	☐	☐	☐
g) I felt that everything I did was an effort.	☐	☐	☐	☐
h) I felt hopeful about the future.	☐	☐	☐	☐
i) I thought my life had been a failure.	☐	☐	☐	☐
j) I felt fearful.	☐	☐	☐	☐
k) My sleep was restless.	☐	☐	☐	☐
l) I was happy.	☐	☐	☐	☐
m) I talked less than usual.	☐	☐	☐	☐
n) I felt lonely.	☐	☐	☐	☐
o) People were unfriendly.	☐	☐	☐	☐
p) I enjoyed life.	☐	☐	☐	☐
q) I had crying spells.	☐	☐	☐	☐
r) I felt sad.	☐	☐	☐	☐
s) I felt that people dislike me.	☐	☐	☐	☐
t) I could not get "going".	☐	☐	☐	☐

APPENDIX C: PARENT REPORT MEASUREMENT TOOLS

Family Adaptability, Partnership, Growth, Affection Resolve (APGAR)

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

Family Inventory of Resources for Management (FIRM): Family Mastery and Health and Extended Family Social Support Subscales

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
s. There are things at home we need to do that we don't seem to get done	0	1	2	3

Family Statements:	**Not at all**	**Minimally**	**Moderately**	**Very Well**
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

Center for Epidemiological Studies Depression Scale (CES-D)

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

APPENDIX D: RESEARCH ETHICS APPROVAL

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Kathy Speechley
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics,Western University

Review Type: Expedited
HSREB File Number: 102819
Study Title: Health-related quality of Life in children with New-Onset Epilepsy: A Long-term Follow-up
Sponsor: Canadian Institutes of Health Research

HSREB Amendment Approval Date: September 14, 2015
HSREB Expiry Date: September 06, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Change in Study Personnel	Incoming Research Assistants (S. Brar & A. Dasiewicz)	2015/08/27
Revised Western University Protocol		2015/08/27
Other	Cover Letter: Time 6 Parent Questionnaire	2015/08/19
Instruments	Time 6 Parent Questionnaire	2015/08/27
Other	Cover Letter: Time 6 Youth 11-17 Questionnaire	2015/08/19
Instruments	Time 6 Youth 11-17 Questionnaire	2015/08/27
Other	Cover Letter: Time 6 Youth 18+ Questionnaire	2015/08/17
Instruments	Time 6 Youth 18+ Questionnaire	2015/08/27
Other	Email/Cover Letter: Time 6 Youth 18+ Questionnaire	2015/08/19
Other	Email/Cover Letter: Time 6 Youth 11-17 Questionnaire	2015/08/19

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]
Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

Erika Basile	Grace Kelly	Mina Mekhail	Vikki Tran
[redacted]	[redacted]	[redacted]	[redacted]

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

APPENDIX E: PRELIMINARY CROSS-LAGGED PANEL AND REGRESSION ANALYSES

In this study, the two-year follow-up was used for the exposure of interest (severity of epilepsy) and the eight-year follow-up was used for the potential family mediators. Thus, these time points were the main focus when determining the casual order between severity of epilepsy and the potential family mediators including family functioning, family resources and parental depressive symptoms. A cross-lagged panel analysis was conducted for each potential mediator in both the study sample (N=129) and the entire HERQULES project sample to compare results and whether associations changed when the sample size was much larger. Additionally, multiple linear regression analyses were conducted to further clarify the casual order between exposure and potential mediators.

Table E-1: Cross-lagged panel analysis examining the relationship between family functioning (APGAR score) and severity of epilepsy (GASE score) for the study sample

Variable	Family Functioning Baseline	Family Functioning 6 Months	Family Functioning 1 Year	Family Functioning 2 Years	Family Functioning 8 Years	Family Functioning 10 Years
Severity of Epilepsy 10 Years	r=-0.31 p=0.08 N=32	r=-0.23 p=0.22 N=31	r=-0.30 p=0.10 N=32	r=-0.32 p=0.07 N=32	r=-0.30 p=0.11 N=29	r=-0.20 p=0.29 N=30
Severity of Epilepsy 8 Years	r=0.13 p=0.49 N=30	r=0.26 p=0.18 N=29	r=-0.11 p=0.55 N=30	r=0.04 p=0.82 N=30	r=0.27 p=0.14 N=29	r=0.24 p=0.21 N=28
Severity of Epilepsy 2 Years	r=-0.16 p=0.08 N=117	r=-0.09 p=0.32 N=116	r=-0.14 p=0.13 N=117	r=-0.17 p=0.08 N=116	r=-0.28 p=0.003 N=112	r=-0.21 p=0.03 N=108
Severity of Epilepsy 1 Year	r=-0.20 p=0.03 N=118	r=-0.24 p=0.01 N=117	r=-0.21 p=0.02 N=118	r=-0.19 p=0.04 N=117	r=-0.21 p=0.03 N=113	r=-0.18 p=0.07 N=110
Severity of Epilepsy 6 Months	r=0.03 p=0.72 N=120	r=-0.04 p=0.65 N=119	r=-0.03 p=0.77 N=120	r=0.01 p=0.96 N=119	r=0.05 p=0.57 N=115	r=0.06 p=0.55 N=110
Severity of Epilepsy Baseline	r=-0.12 p=0.17 N=125	r=-0.03 p=0.74 N=124	r=-0.07 p=0.41 N=125	r=-0.05 p=0.59 N=124	r=-0.07 p=0.42 N=120	r=0.01 p=0.91 N=115

The results (Table E-1) show that severity of epilepsy at two years is correlated with family functioning at eight years ($p<0.005$) but family functioning at two years and severity of epilepsy at eight years are not correlated with each other ($p=0.82$). Thus, early severity of epilepsy may be predictive of subsequent family functioning and not vice versa. However, this finding may have been attributed to the small sample size for severity of epilepsy at eight years. Thus, severity of epilepsy at two years and family functioning at earlier time points (baseline, six months, one year) were also examined and none of these relationships were significant further strengthening the hypothesis of the casual order of the relationship between severity of epilepsy and family functioning.

Table E-2: Cross-lagged panel analysis examining the relationship between family functioning (APGAR score) and severity of epilepsy (GASE score) for all participants in the HERQULES study

Variable	Family Functioning Baseline	Family Functioning 6 Months	Family Functioning 1 Year	Family Functioning 2 Years	Family Functioning 8 Years	Family Functioning 10 Years
Severity of Epilepsy 10 Years	r=-0.17 p=0.26 N=45	r=-0.16 p=0.29 N=44	r=-0.22 p=0.14 N=45	r=-0.35 p=0.02 N=45	r=-0.32 p=0.04 N=40	r=-0.27 p=0.09 N=39
Severity of Epilepsy 8 Years	r=-0.06 p=0.69 N=48	r=0.02 p=0.89 N=47	r=-0.16 p=0.29 N=48	r=-0.03 p=0.83 N=48	r=0.11 p=0.49 N=46	r=0.01 p=0.94 N=39
Severity of Epilepsy 2 Years	r=-0.09 p=0.11 N=314	r=-0.07 p=0.25 N=292	r=-0.06 p=0.30 N=272	r=-0.11 p=0.07 N=254	r=-0.19 p=0.01 N=174	r=-0.21 p=0.007 N=156
Severity of Epilepsy 1 Year	r=-0.19 p=0.0007 N=329	r=-0.14 p=0.02 N=306	r=-0.13 p=0.02 N=280	r=-0.17 p=0.007 N=261	r=-0.13 p=0.10 N=178	r=-0.19 p=0.02 N=160
Severity of Epilepsy 6 Months	r=-0.03 p=0.60 N=335	r=-0.05 p=0.38 N=306	r=-0.08 p=0.20 N=281	r=-0.09 p=0.14 N=261	r=0.07 p=0.35 N=180	r=0.03 p=0.72 N=161
Severity of Epilepsy Baseline	r=-0.10 p=0.07 N=362	r=-0.05 p=0.34 N=327	r=-0.07 p=0.22 N=294	r=-0.10 p=0.11 N=273	r=-0.04 p=0.63 N=186	r=0.00 p=0.97 N=167

The results were consistent when examining the entire HERQULES sample (Table E-3) as those found in the study sample (Table E-2).

Table E-3: Regression analysis to examine the association between severity of epilepsy at two years and family functioning at eight years controlling for baseline family functioning

Variable	Co-efficient (SD)	p-value
Intercept	7.90 (1.12)	<0.0001
2-Year Severity of Epilepsy	-0.52 (0.24)	0.03
Baseline Family Functioning	0.52 (0.07)	<0.0001

A multiple linear regression analysis was conducted to further examine whether severity of epilepsy was associated with future family functioning when taking into account the baseline levels of family functioning. The results (Table E-3) found that severity of epilepsy at the two-year follow-up was associated with family functioning at the eight-year follow-up while controlling for family functioning at the time of epilepsy diagnosis ($p<0.05$). Thus, providing further support along with the cross-lagged panel analysis of the casual order of this relationship.

Table E-4: Cross-lagged panel analysis examining the relationship between family resources (FIRM score) and severity of epilepsy (GASE score) for the study sample

Variable	Family Resources Baseline	Family Resources 6 Months	Family Resources 1 Year	Family Resources 2 Years	Family Resources 8 Years	Family Resources 10 Years
Severity of Epilepsy 10 Years	r=-0.37 p=0.04 N=32	r=-0.32 p=0.08 N=31	r=-0.39 p=0.03 N=32	r=-0.25 p=0.17 N=32	r=-0.47 p=0.01 N=29	r=-0.43 p=0.02 N=30
Severity of Epilepsy 8 Years	r=0.11 p=0.5512 N=30	r=0.18 p=0.36 N=29	r=0.01 p=0.97 N=30	r=0.29 p=0.12 N=30	r=0.01 p=0.97 N=29	r=0.29 p=0.13 N=28
Severity of Epilepsy 2 Years	r=-0.13 p=0.16 N=117	r=-0.10 p=0.30 N=115	r=-0.25 p=0.006 N=116	r=-0.25 p=0.007 N=116	r=-0.30 p=0.001 N=112	r=-0.29 p=0.003 N=108
Severity of Epilepsy 1 Year	r=-0.19 p=0.04 N=118	r=-0.27 p=0.004 N=116	r=-0.33 p=0.0003 N=117	r=-0.21 p=0.02 N=117	r=-0.20 p=0.03 N=113	r=-0.27 p=0.004 N=110
Severity of Epilepsy 6 Months	r=-0.06 p=0.51 N=120	r=-0.12 p=0.18 N=118	r=-0.17 p=0.06 N=119	r=-0.04 p=0.70 N=119	r=-0.01 p=0.94 N=115	r=-0.08 p=0.40 N=110
Severity of Epilepsy Baseline	r=-0.09 p=0.33 N=125	r=-0.09 p=0.31 N=123	r=-0.13 p=0.15 N=124	r=-0.10 p=0.29 N=124	r=-0.09 p=0.30 N=120	r=-0.10 p=0.31 N=115

The results (Table E-4) show that severity of epilepsy at two years and family resources at eight years were significantly correlated (p=0.001) but severity of epilepsy at eight years was not correlated with family resources at two years (p=0.12). However, this finding may have been attributed to the small sample size for severity of epilepsy at eight years. Thus, severity of epilepsy at two years and family resources at earlier time points (baseline, six months, one year) were also examined. While baseline and six-month family resources were not significantly correlated with two-year severity of epilepsy, one-year family resources were significantly correlated with two-year severity of epilepsy ($p<0.01$). Since the correlation between severity of epilepsy at two years and family resources at eight years was stronger, the conclusion was that severity of epilepsy is more likely to precede family resources and thus family resources may be examined as a mediator in this study.

Table E-5: Cross-lagged panel analysis examining the relationship between family resources (FIRM score) and severity of epilepsy (GASE score) for all participants in the HERQULES study

Variable	Family Resources Baseline	Family Resources 6 Month	Family Resources 1 Year	Family Resources 2 Year	Family Resources 8 Year	Family Resources 10 Years
Severity of Epilepsy 10 Years	r=-0.17 p=0.25 N=45	r=-0.13 p=0.42 N=44	r=-0.18 p=0.24 N=44	r=-0.18 p=0.23 N=45	r=-0.40 p=0.01 N=40	r=-0.40 p=0.01 N=39
Severity of Epilepsy 8 Years	r=-0.05 p=0.71 N=48	r=-0.01 p=0.94 N=47	r=-0.06 p=0.67 N=48	r=0.20 p=0.18 N=48	r=0.06 p=0.70 N=46	r=0.16 p=0.34 N=39
Severity of Epilepsy 2 Years	r=-0.08 p=0.18 N=310	r=-0.04 p=0.48 N=292	r=-0.11 p=0.08 N=266	r=-0.11 p=0.08 N=254	r=-0.22 p=0.004 N=174	r=-0.24 p=0.002 N=156
Severity of Epilepsy 1 Year	r=-0.18 p=0.001 N=325	r=-0.18 p=0.001 N=305	r=-0.22 p=0.0002 N=275	r=-0.19 p=0.002 N=260	r=-0.14 p=0.06 N=177	r=-0.19 p=0.01 N=160
Severity of Epilepsy 6 Months	r=-0.12 p=0.03 N=332	r=-0.08 p=0.16 N=306	r=-0.11 p=0.08 N=276	r=-0.10 p=0.12 N=261	r=0.04 p=0.61 N=179	r=0.03 p=0.67 N=161
Severity of Epilepsy Baseline	r=-0.08 p=0.15 N=358	r=-0.04 p=0.51 N=327	r=-0.03 p=0.63 N=289	r=-0.05 p=0.46 N=273	r=-0.04 p=0.63 N=185	r=0.01 p=0.86 N=167

The results examining the entire HERQULES sample (Table E-5) provided further support for severity of epilepsy preceding family resources as severity of epilepsy at the two-year follow-up and family resources at the one-year follow-up were no longer significantly correlated as they were in the study sample ($p=0.08$). Similar to the findings in the study sample, two-year severity of epilepsy and eight-year family resources were significantly correlated ($p<0.005$) but two-year family resources and eight-year severity of epilepsy were not ($p=0.18$).

Table E-6: Regression analysis to examine the association between severity of epilepsy at two years and family resources at eight years controlling for baseline family resources

Variable	Co-efficient (SD)	p-value
Intercept	19.12 (4.00)	<0.0001
2-Year Severity of Epilepsy	-2.00 (0.66)	0.003
Baseline Family Resources	0.68 (0.07)	<0.0001

A multiple linear regression analysis was conducted to further examine whether severity of epilepsy was associated with the future amount of family resources taking into account the baseline amount of family resources. The results (Table E-6) found that severity of epilepsy at the two-year follow-up was associated with family resources at the eight-year follow-up even while controlling for the amount of resources families had at the time of epilepsy diagnosis ($p<0.005$). Thus, providing further support along with the cross-lagged panel analysis of the casual order of this relationship.

Table E-7: Cross-lagged panel analysis examining the relationship between parental depressive symptoms (CES-D score) and severity of epilepsy (GASE score) for the study sample

Variable	Parental Depressive Symptoms Baseline	Parental Depressive Symptoms 6 Months	Parental Depressive Symptoms 1 Year	Parental Depressive Symptoms 2 Years	Parental Depressive Symptoms 8 Years	Parental Depressive Symptoms 10 Years
Severity of Epilepsy 10 Years	r=0.24 p=0.19 N=32	r=0.12 p=0.53 N=31	r=0.20 p=0.27 N=32	r=-0.03 p=0.89 N=32	r=0.11 p=0.57 N=29	r=0.25 p=0.18 N=30
Severity of Epilepsy 8 Years	r=-0.11 p=0.57 N=30	r=0.01 p=0.97 N=29	r=0.03 p=0.86 N=30	r=-0.16 p=0.39 N=30	r=0.20 p=0.29 N=29	r=-0.26 p=0.17 N=28
Severity of Epilepsy 2 Years	r=0.14 p=0.13 N=116	r=0.23 p=0.01 N=115	r=0.24 p=0.009 N=116	r=0.26 p=0.004 N=117	r=0.25 p=0.009 N=112	r=0.22 p=0.02 N=108
Severity of Epilepsy 1 Year	r=0.17 p=0.07 N=117	r=0.29 p=0.002 N=116	r=0.29 p=0.001 N=117	r=0.33 p=0.0002 N=118	r=0.13 p=0.18 N=113	r=0.11 p=0.24 N=110
Severity of Epilepsy 6 Months	r=0.14 p=0.13 N=119	r=0.19 p=0.04 N=118	r=0.16 p=0.09 N=119	r=0.06 p=0.53 N=120	r=0.00 p=1.00 N=115	r=-0.04 p=0.67 N=110
Severity of Epilepsy Baseline	r=0.15 p=0.09 N=125	r=0.08 p=0.40 N=123	r=0.20 p=0.03 N=124	r=0.15 p=0.09 N=125	r=0.01 p=0.92 N=120	r=-0.01 p=0.91 N=115

Severity of epilepsy at two years and parental depressive symptoms at eight years were significantly correlated ($p<0.01$) but severity of epilepsy at eight years and parental depressive symptoms at two years were not correlated ($p=0.4$) (Table E-7). However, this finding may have been attributed to the small sample size for severity of epilepsy at eight years. Thus, severity of epilepsy at two years and parental depressive symptoms at earlier time points (baseline, six months, one year) were also examined. Although baseline parental depressive symptoms were not significantly associated with two-year severity of epilepsy, six-month ($p<0.02$) and one-year parental depressive symptoms ($p<0.01$) were significantly associated with two-year severity of epilepsy. Thus, it is possible that this relationship may be bidirectional.

Table E-8: Cross-lagged panel analysis examining the relationship between parental depressive symptoms (CES-D score) and severity of epilepsy (GASE score) for all participants in the HERQULES study

Variable	Parental Depressive Symptoms Baseline	Parental Depressive Symptoms 6 Months	Parental Depressive Symptoms 1 Year	Parental Depressive Symptoms 2 Years	Parental Depressive Symptoms 8 Years	Parental Depressive Symptoms 10 Years
Severity of Epilepsy 10 Years	r=0.05 p=0.72 N=45	r=0.10 p=0.53 N=44	r=0.13 p=0.41 N=45	r=0.06 p=0.71 N=44	r=0.23 p=0.15 N=40	r=0.28 p=0.09 N=39
Severity of Epilepsy 8 Years	r=0.05 p=0.74 N=48	r=0.28 p=0.06 N=47	r=0.30 p=0.04 N=48	r=-0.07 p=0.64 N=46	r=0.17 p=0.25 N=46	r=-0.03 p=0.86 N=39
Severity of Epilepsy 2 Years	r=0.05 p=0.40 N=312	r=0.16 p=0.005 N=292	r=0.14 p=0.03 N=268	r=0.17 p=0.008 N=253	r=0.22 p=0.003 N=174	r=0.20 p=0.01 N=155
Severity of Epilepsy 1 Year	r=0.12 p=0.03 N=327	r=0.16 p=0.004 N=305	r=0.22 p=0.0002 N=277	r=0.21 p=0.0005 N=260	r=0.05 p=0.48 N=178	r=0.07 p=0.41 N=159
Severity of Epilepsy 6 Months	r=0.08 p=0.14 N=333	r=0.06 p=0.32 N=306	r=0.12 p=0.05 N=278	r=0.03 p=0.61 N=261	r=-0.05 p=0.53 N=180	r=-0.08 p=0.34 N=160
Severity of Epilepsy Baseline	r=0.08 p=0.12 N=361	r=-0.01 p=0.90 N=327	r=0.05 p=0.42 N=291	r=0.11 p=0.08 N=272	r=0.02 p=0.74 N=186	r=-0.05 p=0.55 N=166

The results examining the entire HERQULES sample were similar to those found in the study sample (Table E-8). However, the relationship between eight-year parental depressive symptoms and two-year severity of epilepsy was stronger than the relationship between six-month parental depressive symptoms and two-year severity of epilepsy, whereas in the study sample they were similar. Additionally, even with the larger sample the relationship between parental depressive symptoms at two years and severity of epilepsy at eight years was still not significant (p=0.64). Thus, it is more likely that parental depressive symptoms precede severity of epilepsy.

Table E-9: Regression analysis to examine the association between severity of epilepsy at two years and parental depressive symptoms at eight years controlling for baseline parental depressive symptoms

Variable	Co-efficient (SD)	p-value
Intercept	3.38 (1.55)	0.03
2-Year Severity of Epilepsy	1.59 (0.66)	0.02
Baseline Parental Depressive Symptoms	0.35 (0.07)	<0.0001

A multiple linear regression analysis was conducted to further examine whether severity of epilepsy was associated with future parental depressive symptoms taking into account the baseline parental depressive symptoms. The results (Table E-9) found that severity of epilepsy at the two-year follow-up was associated with parental depressive symptoms at the eight-year follow-up even while controlling for parental depressive symptoms at the time of epilepsy diagnosis ($p<0.05$). Thus, providing further support along with the cross-lagged panel analysis of the casual order between this relationship.

APPENDIX F: SENSITIVITY ANALYSIS

Table F-1: Multivariate regression assessing the relationship between severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders without multiple imputation (n=111)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	1.55 (8.98)	-16.25, 19.36
Severity of Epilepsy	2.19 (0.86)**	0.48, 3.91
Sex	0.06 (1.88)	-3.67, 3.80
Age at Diagnosis	0.79 (0.40)*	0.00, 1.58
Seizure Type	3.08 (1.93)	-0.75, 6.92
Cognitive Problems	-0.07 (2.51)	-5.05, 4.91
Behavioural Problems	-2.49 (2.97)	-8.37, 3.40
Family Income	-0.29 (0.98)	-2.24, 1.65
Parental Living Arrangements	1.30 (2.81)	-4.28, 6.87

Note: R^2=13.8%
*p<0.05, **p<0.02

Table F-2: GEE model assessing family functioning as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders without multiple imputation (n=109)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	10.21 (9.45)	-8.31, 28.73
Severity of Epilepsy	1.85 (1.03)	0.17, 3.86
Sex	-1.11 (1.90)	-4.83, 2.61
Age at Diagnosis	0.80 (0.37)*	0.07, 1.53
Seizure Type	2.73 (1.77)	-0.73, 6.19
Cognitive Problems	0.02 (2.53)	-4.93, 4.97
Behavioural Problems	-1.95 (2.76)	-7.37, 3.47
Family Income	0.13 (0.97)	-1.76, 2.03
Parental Living Arrangements	0.57 (2.85)	-5.01, 6.15
G	-8.62 (4.98)	-18.38, 1.13
M*	-0.50 (0.28)	-1.04, 0.04
G*Severity of Epilepsy	0.30 (0.20)	-0.09, 0.69
G*Sex	1.09 (0.63)	-0.14, 2.33
G*Age at Diagnosis	-0.04 (0.06)	-0.16, 0.08
G*Seizure Type	0.42 (0.39)	-0.34, 1.19
G*Cognitive Problems	-0.06 (0.43)	-0.91, 0.78
G*Behavioural Problems	-0.49 (0.52)	-1.50, 0.52
G*Family Income	-0.36 (0.25)	-0.85, 0.12
G*Parental Living Arrangements	0.77 (0.66)	-0.53, 2.07

*$p<0.05$

Table F-3: GEE model assessing family resources as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders without multiple imputation (n=109)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	13.37 (9.83)	-5.09, 32.64
Severity of Epilepsy	1.78 (0.98)	-0.15, 3.70
Sex	-0.25 (1.81)	-3.80, 3.29
Age at Diagnosis	0.61 (0.37)	-0.12, 1.35
Seizure Type	2.90 (1.79)	-0.60, 6.40
Cognitive Problems	0.70 (2.64)	-4.47, 5.87
Behavioural Problems	-2.51 (2.73)	-7.86, 2.83
Family Income	0.38 (0.95)	-1.50, 2.25
Parental Living Arrangements	-0.21 (2.88)	-5.85, 5.43
G	-11.78 (5.45)*	-22.46, -1.11
M*	-0.20 (0.09)*	-0.38, -0.02
G*Severity of Epilepsy	0.37 (0.23)	-0.08, 0.82
G*Sex	0.24 (0.37)	-0.49, 0.96
G*Age at Diagnosis	0.15 (0.09)	-0.03, 0.32
G*Seizure Type	0.25 (0.39)	-0.50, 1.01
G*Cognitive Problems	-0.74 (0.70)	-2.12, 0.64
G*Behavioural Problems	0.08 (0.49)	-0.88, 1.03
G*Family Income	-0.60 (0.33)	-1.24, 0.04
G*Parental Living Arrangements	1.55 (0.90)	-0.22, 3.33

*p<0.05

Table F-4: GEE model assessing five-year seizure freedom as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders without multiple imputation (n=110)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	-2.83 (7.82)	-18.15, 12.49
Severity of Epilepsy	0.84 (1.07)	-1.26, 2.94
Sex	0.67 (1.82)	-2.90, 4.25
Age at Diagnosis	0.73 (0.33)*	0.09, 1.38
Seizure Type	2.87 (1.74)	-0.54, 6.29
Cognitive Problems	-1.33 (2.62)	-6.46, 3.80
Behavioural Problems	-1.90 (2.87)	-7.53, 3.73
Family Income	-0.27 (0.92)	-2.07, 1.53
Parental Living Arrangements	0.67 (2.47)	-4.17, 5.51
G	7.11 (3.43)*	0.38, 13.84
M*	6.33 (2.18)**	2.06, 10.60
G*Severity of Epilepsy	1.34 (0.47)**	0.42, 2.25
G*Sex	-0.37 (0.56)	-1.46, 0.72
G*Age at Diagnosis	0.04 (0.12)	-0.19, 0.27
G*Seizure Type	-0.03 (0.55)	-1.11, 1.05
G*Cognitive Problems	0.94 (0.69)	-0.42, 2.29
G*Behavioural Problems	-1.32 (0.95)	-3.19, 0.55
G*Family Income	-0.07 (0.28)	-0.62, 0.48
G*Parental Living Arrangements	0.32 (0.82)	-1.30, 1.94

*p<0.05, **p<0.005

Table F-5: GEE model assessing AED use as a mediator between the relationship of severity of epilepsy and depressive symptoms controlling for potential demographic and clinical confounders without multiple imputation (n=109)

Variable	Co-efficient (SE)	95% Confidence Interval
Intercept	8.81 (10.00)	-10.79, 28.42
Severity of Epilepsy	1.73 (1.10)	0.42, 3.88
Sex	-0.49 (1.82)	-4.07, 3.08
Age at Diagnosis	0.72 (0.37)*	0.00, 1.44
Seizure Type	4.06 (1.74)**	0.66, 7.46
Cognitive Problems	-0.80 (2.66)	-6.01, 4.42
Behavioural Problems	-1.90 (2.89)	-7.55, 3.76
Family Income	-0.82 (0.95)	-2.69,1.05
Parental Living Arrangements	0.88 (2.82)	-4.65, 6.42
G	-6.51 (5.89)	-18.05, 5.04
M*	-2.79 (2.49)	-7.67, 2.09
G*Severity of Epilepsy	0.49 (0.44)	-0.37, 1.35
G*Sex	0.06 (0.23)	-0.39, 0.51
G*Age at Diagnosis	0.09 (0.10)	-0.10, 0.28
G*Seizure Type	-0.33 (0.33)	-0.97, 0.32
G*Cognitive Problems	0.55 (0.56)	-0.54, 1.64
G*Behavioural Problems	-0.68 (0.72)	-2.09, 0.73
G*Family Income	0.16 (0.18)	-0.18, 0.51
G*Parental Living Arrangements	0.36 (0.41)	-0.45, 1.16

*p<0.05, **p<0.02

Curriculum Vitae

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Post-secondary Education and Degrees	Western University London, Ontario, Canada 2015-2017 MSc.
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Honours And Awards	Queen Elizabeth II Graduate Scholarship in Science and Technology 2016-2017
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	York University Renewable Entrance and Continuing Student Scholarship 2011-2015
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Samanpreet Brar, Kelly K. Anderson, Mark A. Ferro, Kathy N. Speechley. Depressive Symptoms in Adolescents and Young Adults with Epilepsy 10 Years after Diagnosis: A Test of the Stress Process. Canadian Society for Epidemiology and Biostatistics Conference 2017*, The Banff Centre, Banff, Alberta. June 1, 2017*. (Oral presentation)

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