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Epilepsy worry in adolescents and young adults with childhood-onset epilepsy ten years after diagnosis

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Abstract

This thesis explored the extent to which adolescents and young adults (AYAs) with childhood-onset epilepsy experience epilepsy worry 10 years after diagnosis and its association with AYAs' clinical, demographic, and family characteristics. It also explored the extent to which epilepsy worry correlates with anxiety and depression. Data were derived from the Health-Related Quality of Life in Children with Epilepsy Study, a multicenter prospective cohort study that followed children with newly-diagnosed epilepsy for 10 years after diagnosis. At the 10-year follow-up, about 40% of 130 AYAs had experienced at least some epilepsy worry within the past four weeks. A binomial-gamma hurdle model found that 5-year seizure freedom status and current anti-epileptic drug treatment were associated with epilepsy worry. Epilepsy worry was weakly and moderately correlated with anxiety and depression, respectively. These findings highlight epilepsy worry as a potential distinct intervention target for improving the mental health of AYAs with childhood-onset epilepsy.

Keywords

Childhood-onset epilepsy, disease-specific mental health, worry, epilepsy worry, adolescents, young adults, longitudinal study.

Summary for Lay Audience

The unpredictable nature of seizures in epilepsy may provoke *epilepsy worry*—a state of worry specific to future seizures and their consequences that could influence the mental health of people with epilepsy. The aims of this thesis were to assess the extent to which adolescents and young adults (AYAs) experience epilepsy worry 10 years after their epilepsy diagnosis in childhood, and to identify possible risk factors for epilepsy worry. This thesis also assessed the extent to which AYAs' epilepsy worry correlates with anxiety and depression. Data for this thesis were derived from the Health-Related Quality of Life in Children with Epilepsy Study, a multicenter prospective cohort study that followed children with newly-diagnosed epilepsy for 10 years after diagnosis. While the majority of the 130 AYAs studied were not experiencing epilepsy worry, which is consistent with the generally favourable long-term seizure outcome for childhood-onset epilepsy, about 40% of these AYAs had experienced at least some epilepsy worry within the past four weeks. AYAs who had not achieved seizure freedom and those who were currently taking anti-epileptic drugs have higher odds of experiencing any epilepsy worry, and AYAs who were currently taking anti-epileptic drugs were more likely to experience higher levels of epilepsy worry. Anxiety was found to be weakly correlated with epilepsy worry, while depression was moderately correlated with epilepsy worry. This means that epilepsy worry is related to anxiety and depression but is partially distinct. These findings suggest that epilepsy worry should be examined as its own aspect of mental health in people with epilepsy, both in research and in clinical practices. More research is needed to understand the relationship between anti-epileptic drugs and epilepsy worry. Healthcare professionals could consider screening AYAs in remission to identify those who still experience epilepsy worry and offer reassurance to reduce their worry.

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List of Abbreviations

AED	Anti-epileptic drug
APGAR	Family Adaptability, Partnership, Growth, Affection and Resolve
AYA	Adolescent and young adult
BECRS	Benign epilepsy of childhood with rolandic spikes
CES-D	Center for Epidemiologic Studies Depression Scale
CHEQOL	Health Related Quality of Life Measure for Children with Epilepsy
CHQ	Child Health Questionnaire
DRE	Drug-resistant epilepsy
FILE	Family Inventory of Life Events & Changes
FIRM	Family Inventory of Resources for Management
GASE	Global Assessment of Severity of Epilepsy
HERQULES	Health-Related Quality of Life in Children with Epilepsy Study
IAA	Interictal anticipatory anxiety
IBE	International Bureau for Epilepsy
ILAE	International League Against Epilepsy
MICE	Multiple imputation by chained equations
(HR)QoL	(Health-related) Quality of life
QOLIE	Quality of Life in Epilepsy Inventory
STAI	Spielberger State-Trait Anxiety Inventory

Chapter 1

1 Introduction

Epilepsy is a neurological disease with its most defining feature being recurrent and unprovoked seizures. Seizures are unpredictable in nature, and the severity can range from a brief loss of consciousness—absence seizures—to generalized tonic-clonic seizures where the loss of consciousness is followed by strong tonic muscle spasms and intense jerking movements. The consequences of having seizures, the side effects of having treatments for seizures, and conditions that are co-morbid with epilepsy can all impose challenges on an individual's life, from influencing school or work and placing restrictions on recreation or social life, to adding strains on family relationships. Due to the unpredictability of seizures, it is understandable that individuals with epilepsy tend to worry about the occurrence of future seizures, referred to as *epilepsy worry*. Worry is a natural response to anticipated future problems, and excessive worrying can negatively influence an individual's emotional and physical health. When it comes to worrying about epilepsy, excessive worrying can place additional emotional burden on an individual's attempt to cope with the condition and further restrict their lives and activities.

As with other emotions, how much a person worries about their epilepsy and seizures can be influenced by a wide range of factors. Clinical characteristics such as when the person last experienced a seizure or the severity of the person's seizures are likely to have an influence on epilepsy worry. Demographic characteristics (e.g., the person's sex) or family characteristics (e.g., the amount of resources available to families to help with adaptation to stressful life events) could also contribute to the person's extent of worry. Understanding the extent to which people with epilepsy experience epilepsy worry and the relationship between epilepsy worry and the possible influencing factors could help identify a subgroup of individuals who are at increased risk of epilepsy worry and inform efforts to develop effective interventions to address their worry.

The aims of this thesis were to assess the extent to which people with childhood-onset epilepsy, specifically adolescents and young adults (AYAs), experience epilepsy worry, and to assess the relationship between epilepsy worry and AYAs' clinical, demographic, and family characteristics. Chapter 2 provides a more detailed review of the literature on epilepsy and an overview on the current state of knowledge regarding epilepsy worry. Chapter 3 presents the specific objectives for the thesis, and introduces the conceptual framework used to guide the data analysis in this thesis. Chapter 4 provides details of the methodology used in this thesis, including the source of data, measurement of variables, and data analysis plans. Chapter 5 presents the study findings, and Chapter 6 summarizes and discusses the study results.

The data analyzed in this thesis arose from the Health-Related Quality of Life in Children with Epilepsy Study (HERQULES), described in more detail in Chapter 3.

My role in the study included: Developing research objectives for this thesis, conducting a literature review pertaining to the thesis objectives, conducting statistical analysis under the supervision of my thesis committee, and creating summary reports of the study findings and making conclusions based on the findings.

Chapter 2

2 Background

This chapter provides background information about epilepsy and epilepsy worry, which motivated this thesis. Section 2.1 provides a broad picture on epilepsy and its epidemiology, followed by an overview of worry as an emotion and the literature on epilepsy worry in section 2.2. Section 2.3 discusses the impact of a child's epilepsy on the family and the potential influence of parent's worry on child's health. The chapter finishes with a summary of the limitations of past studies on epilepsy worry in section 2.4.

2.1 Epilepsy

Epilepsy is a neurological disease of the brain with a predisposition to generate recurrent seizures. According to the most recent definition of epilepsy provided by the International League Against Epilepsy (ILAE) in 2014, a person is considered to have epilepsy if any of the following three conditions are met (1):

1. "At least two unprovoked (or reflex) seizures occurring >24 h apart," or
2. "One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years," or
3. "Diagnosis of an epilepsy syndrome," which could occur even if the risk of subsequent seizures are low, as long as specific features for the syndrome, such as the age when seizure begin, seizure types, and EEG findings, are present.

For people with epilepsy, the ideal outcome is to be free of seizures without being dependent on medication. Based on the recently adopted definition of epilepsy resolution, epilepsy is considered to be resolved when an individual with an age-dependent epilepsy syndrome has past the age range for the syndrome, or if the individual has been seizure-free for at least 10 years without using anti-seizure medications for at least the most recent 5 years (1).

The primary method of treatment for epilepsy is anti-epileptic drugs (AEDs). Unfortunately, approximately a third of people with epilepsy do not respond to AEDs and continue to experience seizures (2). Alternative treatment options are available for these people with drug-resistant epilepsy (DRE), including dietary modifications (ketogenic diet, modified Atkins diet, or low glycemic diet), vagal nerve stimulation, and surgical intervention.

2.1.1 Epilepsy in Children

Epilepsy is the most common neurological condition in children. According to a recent review article summarizing the incidence and prevalence of epilepsy in children around the world (3), the incidence of epilepsy in children is 41 to 187 per 100,000 per year with a higher incidence in low and middle income countries. Incidence is highest during the first year of life and gradually declines to a level similar to that of adults by approximately 10 years of age. The prevalence of epilepsy in children is estimated to be 3.2 to 5.5 per 1,000 in high income countries and 3.6 to 44 per 1,000 in low and middle income countries (3). In Canada, the prevalence of epilepsy in children (birth to 15 years of age) is estimated to be 2.3 to 5.3 per 1000 (4).

The long-term seizure outcome for childhood-onset epilepsy is generally favourable, and approximately two-thirds of childhood-onset epilepsies will enter 5-year terminal remission (5–7). However, there is a possibility of relapse even after having a long period of remission, and some of these relapses may become intractable (5,6). Although the possibility of relapse after seizure remission is low, a guarantee of permanent seizure-free status cannot be made.

2.1.2 Comorbidity

Epilepsy involves more than just recurrent seizures. The ILAE and the International Bureau for Epilepsy (IBE) define epilepsy as a condition that is also characterized by its neurobiological, cognitive, psychological, and social consequences (8). A number of studies have been conducted to evaluate the risk of comorbidities in children with

epilepsy compared to the general population or children with other chronic conditions. A national survey from the United States reported that children with active epilepsy are at significantly higher risk of psychological and developmental comorbidities, when compared to children who have never been diagnosed with epilepsy (9). These comorbidities include depression, anxiety, attention deficit hyperactivity disorder (ADHD), developmental delay, and autism spectrum disorder (ASD). Children with epilepsy also demonstrate poorer social competence and more academic difficulties compared to those without epilepsy (9). The same survey found that children who had a previous diagnosis of epilepsy but who were not having seizures currently had intermediate levels of risk for these comorbidities and difficulties (9). In a nationwide study in Norway, 78% of children with epilepsy (birth to 17 years) had at least one comorbid disorder (either medical, neurological, developmental, or psychiatric) on record, compared to only 30% of children in the general population (10). When focusing on developmental and psychiatric disorders, these conditions were reported in 43% of children with epilepsy, compared to only 7% in the general population (10). This increased risk of psychiatric disorders was also found in a nationwide survey in Britain, where children with epilepsy aged 5 to 15 years had a prevalence of psychiatric disorders (37%) that was much higher compared to those with diabetes (11%) or controls (9%) (11).

Comorbid conditions associated with epilepsy are increasingly recognized as important factors for long-term psychosocial outcomes. These comorbid conditions may share causes or risk factors with epilepsy, be the causes of epilepsy, or are the consequence of seizures or anti-epileptic treatment. Comorbid conditions in a large proportion of children with epilepsy impose significant impacts on both the children and society. They interfere with social, cognitive, and psychological development in children with epilepsy, and have been found to influence their quality of life (QoL) more than seizure-related characteristics like remission status and severity of epilepsy (12). Furthermore, having psychiatric and developmental comorbidities increases the utilization of health resources—including outpatient neurology visits, emergency department visits, and

hospitalizations—among children with epilepsy, and the risk of such costly utilization increases with the number of comorbidities (13). Although psychiatric comorbidities require attention and adequate management, the need for mental health services in children with epilepsy is often unmet (14). These unmet needs occur more frequently in these children compared to those without a diagnosis of epilepsy (9), and continue to be experienced two years after the child's first seizure (15). Such unmet needs can exacerbate the impact of psychiatric comorbidities on both children and society. Thus, it is important to increase awareness of psychiatric comorbidities associated with epilepsy in children to reduce the impact of these psychiatric comorbidities.

2.2 Epilepsy Worry

2.2.1 Worry

Worry is a common response to stressful events, representing an attempt to problem-solve an issue with uncertain future outcomes that contains the possibility of one or more negative outcomes (16). However, worrisome thoughts are often unproductive or counterproductive and can prolong or magnify negative affect (16,17). Brosschot and colleagues (16) refer to worry as a cognitive representation of stressors that triggers the physiological stress response, including enhanced activity across numerous physiological parameters. These authors proposed the "perseverative cognition hypothesis" where stressful events affect somatic health through the prolonged activation of stress-related physiological activity, facilitated by worrying, that can ultimately result in somatic health problems. The mediating role of worry in the effect of stress on somatic health has been supported by other studies (18,19). Additionally, worry has been found to mediate the effect of stress on cognition (18).

2.2.2 Worry and Anxiety

Worry is often viewed as the same construct as anxiety, and the two terms are often used interchangeably. Worry is also the defining feature of anxiety disorders. For example, generalized anxiety disorder (GAD) is an anxiety disorder that includes

"persistent and excessive anxiety and worry about various domains, including work and school performance, that the individual finds difficult to control" (20). There are, however, subtle differences between the two constructs. Worry appears to be primarily cognitive in nature (21,22). On the other hand, anxiety is generally conceptualized as a global construct that includes affective, cognitive, and physiological elements (23), although there have been attempts to differentiate worry and anxiety by ascribing somatic responses to anxiety and cognitive processes to worry (22,24). Zebb and Beck (22) have noted that most measures developed for anxiety include both cognitive and somatic items, which unfortunately complicates the effort to establish a distinction between worry and anxiety.

2.2.3 Epilepsy Worry

Seizures in epilepsy may occur anytime without warning signs. People with epilepsy may also suffer from seizure-related injuries that are not easily preventable (25), with the risk of injury being significantly higher compared to their siblings without epilepsy (26). The unpredictability of seizures and the potential for physical injury related to the occurrence of seizures during everyday activities may provoke a state of worry specific to future seizures and their consequences in people with epilepsy. Disease-specific mental health, specifically distress, has been previously investigated. One notable example is diabetes-distress. Diabetes distress refers to an emotional response (including worries, concerns, and fears) to the diabetes condition which is chronic in nature with demanding management (27). It has been established to be distinct from depression in people with diabetes (27). Disease-specific distress has also been examined in inflammatory bowel disease, where it was found to be distinct from anxiety, depression and stress (28), as well as in asthma, where an instrument has been developed to assess the specific distress (29).

The concept of epilepsy-specific worry has been mentioned in the literature, although not explored in detail. Worry is a common theme in qualitative studies of people with epilepsy. In a qualitative study of children and adolescents with intractable epilepsy,

worry regarding the unpredictability of seizures and loss of control emerged as one of the key findings regarding the impact of epilepsy on quality of life. These children and adolescents experienced “periods of intense emotional distress that they attributed largely to the unpredictability of their seizures and loss of control over their bodies” (30). Worry tends to be strongly associated with children’s attitude toward their illness (31). When levels of worry are high, the excessive worrying may affect children’s emotional well-being as well as influence their psychosocial adjustment to their illness. Self-efficacy in managing seizures in children with epilepsy may also be compromised when they worry a lot about their illness (32).

There has not been a uniform term to refer to the concept of epilepsy-specific worry. In a review article, Beyenburg and colleagues (33) attempted to distinguish types of epilepsy-related anxiety symptoms and comorbid anxiety that is unrelated to epilepsy. One of the types of epilepsy-related anxiety symptoms proposed was *interictal anticipatory anxiety (IAA)*, which refers to “a combination of psychological worries about the disorder and its complications” (33). If left unaddressed, it is possible for IAA to lead to the development of a number of mental disorders, or initiate a vicious cycle of increased levels of stress leading to increased seizure frequency and then increased IAA (34). The concept of epilepsy-specific worry has also been referred to as *seizure worry* and incorporated into an instrument for evaluating the quality of life in people with epilepsy (35).

As discussed previously, worry is a construct distinct from anxiety, although the distinction has yet to be fully clarified in the context of epilepsy. Also, epilepsy is a disease that is characterized by not only seizures but also by its neurobiological, cognitive, psychological, and social consequences (8). As such, both the terms IAA and seizure worry do not seem to adequately capture the full scope of the concept of epilepsy-specific worry. Thus, for the purpose of this thesis, the term *epilepsy worry* is proposed to refer to an apprehensive expectation of future seizures and the consequences of epilepsy.

It is increasingly recognized that people with epilepsy have a higher risk of psychiatric comorbidities, including anxiety and depression (36). When examining the mental health care needs of people with epilepsy, epilepsy worry may be attributed to anxiety or related conditions or be considered as part of the normal adaptation process to epilepsy. Worrying thoughts have been found to be the most prevalent symptoms of anxiety among people with epilepsy, which could complicate the attempt to separate the two (37). However, there could be value in distinguishing those who are experiencing epilepsy worry from those experiencing anxiety or depression, as they may require different interventions to help them cope with their condition. For example, McNelis and colleagues (38) suggested that providing information to children with epilepsy that is tailored to their specific needs could help reduce the fears and worries that the children are experiencing due to incomplete or incorrect information, and may improve their attitude toward both their condition and themselves.

2.2.4 Epilepsy Worry, Adolescence, and Stigma

Adolescence is a critical period of development marked by profound physical, psychological, and social transformations. It is also an especially vulnerable period—about three quarters of mental disorders have their onset by 24 years of age (39). During this stage of life, adolescents are faced with adjustment tasks such as identity formation, increased life responsibilities, and gaining independence. For adolescents with epilepsy, they must manage the increased stress from having to adjust to additional challenges and limitations from their condition that could affect their development and functioning. Examples of these additional challenges include difficulty attaining independence, affected academic performance, and restrictions on driving and leisure activities (40). Concerns expressed by adolescents living with epilepsy were often related to establishing independence, future choices, and decision making (41).

A main challenge that adolescents with epilepsy often face is the stigma associated with epilepsy, standing as one of the barriers to achieve a satisfying life. It has been established that stigma operates on three different levels: internalized, interpersonal,

and institutional stigma (42). In past literature, internalized stigma has also been referred to as felt stigma, perceived stigma, or perceptions of stigma, all of which refer to the stigma felt within the person reflecting their feelings, thoughts, beliefs and fears about being different. All three levels of stigma could occur in the lives of people with epilepsy, and its background and impact within the epilepsy context has been discussed in detail in prior literature (43). For adolescents with epilepsy, stigma is prevalent in their social environment and is especially impactful in this stage of life. A large survey of adolescents in the United States revealed that these adolescents are often unfamiliar with epilepsy and hold misconceptions about the illness, and the findings suggest that these negative peer attitudes could create a difficult social environment that contributes to internalized stigma among adolescents with epilepsy (44). Similar to others of similar age, adolescents with epilepsy are likely to be sensitive to peer norms and feelings of being different or singled out. They may limit the disclosure of their condition in order to feel less different or less interpersonal stigma around their peers, and this fear can consequently result in internalized stigma.

There have been improvements in public attitudes toward epilepsy over the recent years (45), but stigma continues to adversely impact the lives of people with epilepsy. Traditional ideas on epilepsy continue to contribute to public misperceptions and negative attitudes (43,45), subsequently leading to people with epilepsy continuing to experience discrimination or fear of being different due to their condition. Internalized stigma has been found to be associated with poorer QoL in people with epilepsy (46). For children and adolescents with epilepsy, internalized stigma has been found to be associated with lower self-esteem, poorer self-concept, and increased depression and anxiety (47–49). Internalized stigma has also been found to be associated with epilepsy worry. In a study that sought to identify factors most strongly associated with internalized stigma in children and adolescents with epilepsy, greater child fear and worry about epilepsy were associated with higher levels of internalized stigma (50). Based on their findings, the authors suggested that identifying children who are fearful and worried about their epilepsy could help target those who are at risk of internalized

stigma, and that interventions which address these fears and worries could help reduce internalized stigma. For those with childhood-onset epilepsy, although the long-term outcome is generally favourable and many will have outgrown their seizures by the time they reach adolescence, they may continue to experience epilepsy worry due to the unpredictability of seizures and the possibility of relapse even after long remission time. As such, it could be beneficial to examine the levels of epilepsy worry in people with childhood-onset epilepsy, as they may continue to experience internalized stigma after seizure remission, which would impact development and functioning.

2.2.5 Epilepsy Worry in Published Instruments

The concept of epilepsy worry has been incorporated into several instruments for use in people with epilepsy. The Epilepsy Surgery Inventory (ESI-55) is designed to measure QoL in candidates for epilepsy surgery and includes an item regarding epilepsy worry as a part of its "health perception" scale (51). The Quality of Life in Epilepsy (QOLIE) inventory expanded upon the ESI-55 to make the instrument applicable to people with epilepsy who are not candidates for surgery, and developed a more extensive epilepsy worry subscale in both its original 89-item version and in its more commonly used 31-item version (35,52). The QOLIE-31 includes a "seizure worry" subscale that examines how worried an individual is regarding seizures and related events, such as injuries and social embarrassments. In the process of adapting the QOLIE inventory for adolescents, the seizure worry items from the QOLIE-89 did not meet the minimal statistical standards and were excluded from the subscales and the total score; however, several of the epilepsy worry items were retained as optional items in the final version, QOLIE-AD-48, due to the potential importance for evaluating individual cases (53). The concept of epilepsy worry was also included in the Health Related Quality of Life Measure for Children with Epilepsy (CHEQOL-25) instrument, where its "worries and concerns" subscale evaluates children's and youths' perceptions on epilepsy-related restrictions, risks and injuries, and concerns about their parents' worries (54). Lastly, the Child Report of Psychosocial Care Scale was developed to assess the psychosocial care needs

of children with seizures in the clinical setting, and includes a “concerns and fears” section that examines how often the children were concerned or worried about their seizures and related events (55).

Instruments that include the epilepsy worry concept have been developed, with sound psychometric properties established, and incorporated into practice. However, the operationalization of epilepsy worry is inconsistent in the subscales concerning epilepsy worry across these instruments. To date, a separate instrument has not been developed to assess epilepsy worry specifically and include all possible aspects of epilepsy worry; an optimal choice for assessing epilepsy worry has yet to be established.

2.3 Parents’ Worry

2.3.1 Impact of Children’s Epilepsy on Families

Childhood-onset epilepsy not only affects the child but also affects the child’s family. Families of children with epilepsy often face more difficulties compared to other families, including in quality of the parent-child relationship, family stress and functioning, and family cohesion (56). For parents, caring for children with epilepsy is a challenging and stressful responsibility and the uncertainty related to when the next seizure may occur, as well as to the child’s current and future state of health, adds additional stress and burden. Due to the caregiving burden, parents of children with epilepsy often experience impaired QoL (57,58), although it has been found that the long-term health-related quality of life (HRQoL) of mothers was comparable to women in the general population many years after their child’s epilepsy diagnosis (59). Parents of children with epilepsy also frequently experience symptoms of depression (60,61) and anxiety (61) above the threshold where individuals are considered to be at-risk for a clinical diagnosis, and their scores are generally higher than parents of healthy children (58,60,61). Mothers are at an especially increased risk of depression, anxiety, and stress compared to fathers in response to the burden of caring for children with epilepsy, as they are often the primary caregivers (62).

2.3.2 Parents' Worry and Children's Outcomes

When factors such as family functioning and parents' emotional well-being are impacted by the diagnosis of epilepsy and the burden of caring for children with epilepsy, these factors can in turn influence the child. For example, the same review that reported symptoms of anxiety in parents of children with epilepsy also found that increased parents' anxiety is associated with reduced child HRQoL and worse adaptive behaviour (61). Parents' perception of the health of their child with epilepsy can also be influenced by the impact that epilepsy has on parents. Due to the social stigma, unpredictability of seizures, and burden of managing the disease, parents of children with epilepsy may express heightened worry and concerns about the child, possibly more than the child's own concerns. The discrepancies based on perspectives can be seen by comparing parent proxy-reports and child self-reports. For example, when evaluating a child's HRQoL, parents of children with epilepsy often report their child having lower levels of HRQoL and higher levels of behavioral problems compared to sibling controls, while the children report levels comparable to sibling controls (63,64). Most of the discrepancy between parent and child report could be accounted by the emotional impact of children's epilepsy on parents (64), although it has been found that maternal depression does not contribute to an under-estimation of the child's health (65).

Parents of children with epilepsy play a key role in determining how their child will adapt to their condition. When parents worry excessively and hold a pessimistic attitude toward their child's health and QoL, they may adopt an over-protective or over-controlling parenting style, placing restrictions on their child's activities and limiting their child's autonomy (66). This parenting style could in turn influence their child's psychosocial well-being (66,67). Children with epilepsy have also been found to be significantly more dependent on their mothers than children in the general population or those with diabetes (68), and this dependency could partly be accounted for by parental overprotection (69). When children experience overprotective parenting and are dependent on their caregivers, their self-management capability is likely to be

compromised (69). An over-protective parenting style, along with its effect on the child's psychosocial well-being and development, influences children's adjustment to their epilepsy and development of the skills necessary as they step into young adulthood.

2.4 Limitations of Past Studies

Past studies that focused on identifying epilepsy worry are often qualitative in nature, describing how people with epilepsy feel about their condition. In most of the quantitative studies, epilepsy worry was included as part of a measure, most often those assessing QoL such as the QOLIE and CHEQOL-25, and was assessed as a predictor for a different outcome of interest. There has been a lack of studies measuring epilepsy worry as an outcome. As well, the extent to which people with epilepsy experience epilepsy worry and the relationships between epilepsy worry and possible risk factors have not been systematically explored. This could possibly be due to the inconsistencies regarding what should be covered by this concept, and the absence of an instrument developed specifically for epilepsy worry that includes all possible aspects. In addition, research focus has been placed more heavily on individuals with severe or poorly-controlled epilepsy. Those with well-controlled or less severe epilepsy, or those who have been in remission or achieved resolution, were often excluded from studies. Due to the unpredictability of seizures and the possibility of relapse after remission, these individuals may continue to experience epilepsy worry and its associated impacts and should be included in studies on epilepsy worry to provide more insight on its risk factors and extent of impact.

Chapter 3

3 Study Objectives and Conceptual Framework

This chapter presents the objectives of this thesis and the conceptual framework that was used to guide the data analysis.

3.1 Study Objectives

The overall goal of this thesis was to describe epilepsy worry in AYAs with childhood-onset epilepsy and the worries experienced by their parents. The specific objectives were as follows:

1. To describe the extent to which AYAs with childhood-onset epilepsy experience epilepsy worry, and to explore its associations with epilepsy severity and other clinical, demographic, and family characteristics.
2. To explore the extent to which epilepsy worry correlates with anxiety and depression in AYAs with childhood-onset epilepsy.
3. To explore the extent to which parents of AYAs with childhood-onset epilepsy experience worry regarding their child's health, and whether it mediates the effect of epilepsy severity on AYAs' epilepsy worry.

3.2 Conceptual Framework

The stress process model was used to guide the data analysis in this thesis (70). The stress process model is a conceptual paradigm that has provided theoretical foundations for many sociological studies on stress and mental health since it was introduced. The focus of the model is to understand how stress arises to affect mental health outcomes, and the interrelationship among the factors that contribute to this process (70–72). The stress process model acknowledges the temporal nature of the interrelationships among many of these factors, and helps to provide a better understanding of the relationship between the exposure and the outcome of interest. The perspectives of the stress process arose from a study conducted by Pearlin and colleagues (70) analyzing the effects of involuntary job loss on depression. The study found that the event of

involuntary job loss led to secondary stressors including financial and marital strain, which largely accounted for the effect of involuntary job loss on depression. The same study also found that personal and social resources, such as social support, mastery, and self-esteem, played a role in mediating and moderating the effects of stressors on depression. Following the introduction of this stress process perspective, the model has been successfully applied in many epidemiologic studies on mental health outcomes, including depression in people with physical disability and matched controls (73), depression in the general population (74), depression and physical health in family caregivers of dementia patients (75), depression and life satisfaction in spousal caregivers of hospice patients with dementia or lung cancer (76), distress in caregivers of dementia patients (77), and studies on HRQoL, emotional well-being, and cognitive functioning in children with epilepsy (78–80). The stress process model has not been previously applied in studies on epilepsy worry, but it could offer a framework for research on epilepsy worry, given its track record of successful applications to studying the effects of stress on mental health outcomes.

The stress process model consists of three core components: stressors, stress mediators, and stress outcomes. Stressors are conditions that may impact mental health and can give rise to secondary stressors. Stressors typically arise out of two circumstances, the occurrence of discrete life events and the presence of chronic problems, and these two sources of stress work synergistically to produce stress outcomes (70–72). The production of stress outcomes by these stressors can be direct, or they can act indirectly through stress mediators. Lastly, the stress process model acknowledges that the underlying characteristics of each individual, such as age, sex, socioeconomic status, and other background and contextual factors, could lead to variations in the stress outcome (70–72).

Figure 3.1 presents the theoretical framework used to guide this thesis. For the purpose of this thesis, the initial stressors to produce a stress outcome were the diagnosis of epilepsy and living with epilepsy. The severity of the AYAs' epilepsy was used as a proxy

to represent the amount of stress experienced from these sources. Epilepsy severity then acts directly or indirectly through parents' worry to produce the outcome of interest, epilepsy worry. The background factors that could possibly affect the stress outcome and were assessed in this thesis include both clinical characteristics (recency of last seizure, current use of AEDs, seizure type, behavioural comorbidities, cognitive comorbidities), and demographic characteristics (AYA age, AYA sex, parents' age, parents' depressive symptoms, parents' marital status, family income). Psychosocial aspects of the family environment have also been previously found to be associated with behavioural and psychiatric problems (56,81), psychosocial adaptation (82), and overall HRQoL (83) in children with epilepsy, and could possibly influence a child's psychological adjustment to epilepsy more than clinical factors (84). As such, it would be beneficial to also include factors on the psychosocial aspects of the family environment in the model and explore whether these factors have a potential effect on the AYAs' epilepsy worry. Lastly, anxiety and depression were included as constructs overlapping with the stress outcome epilepsy worry. The overlap between worry and anxiety was discussed in the previous chapter. Depression has been conceptualized as an emotion that is distinct from anxiety but has common characteristics (85). Depression has been shown to be associated with both worry and anxiety in past studies and is significantly correlated with anxiety in people with epilepsy, thus it is also included in the model for assessing the extent of correlation among these three constructs (21,37,86,87).

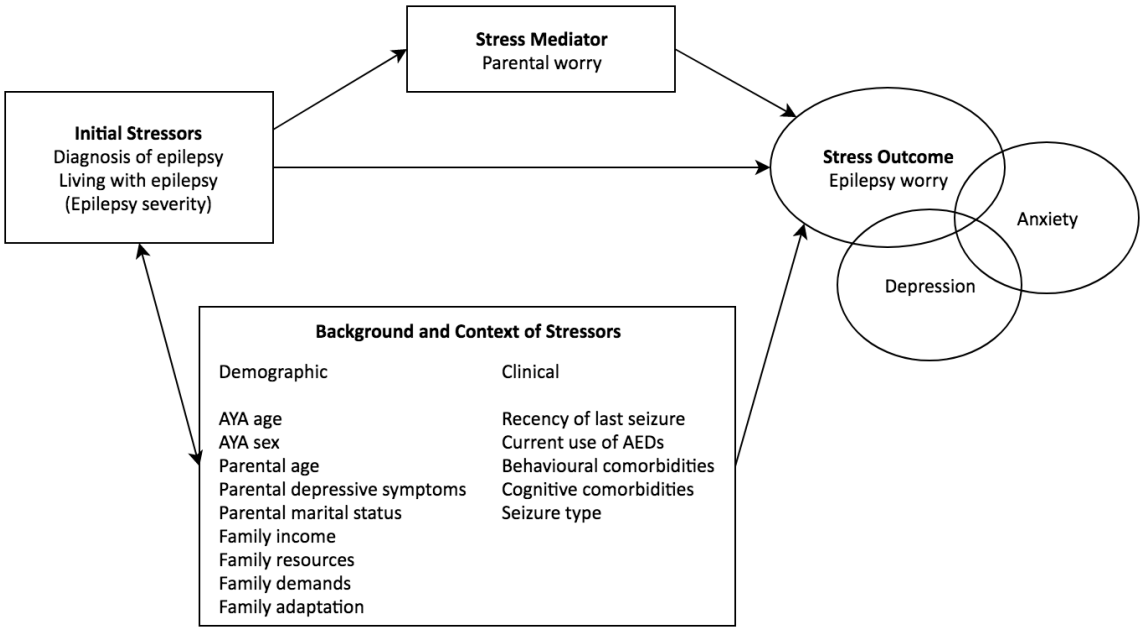

Figure 3.1: Conceptual framework for this thesis.

Chapter 4

4 Methods

This chapter describes the methodology employed in this thesis. Section 4.1 presents details on the source of the data, followed by descriptions of measurement tools used in this thesis in section 4.2. The chapter closes with a description of the statistical analysis methods in section 4.3.

4.1 Data Source and Sample

The data used in this thesis arose from HERQULES, a national multicenter prospective cohort study which followed children in Canada with newly diagnosed epilepsy for approximately 10 years after diagnosis. There were two phases of HERQULES: The initial phase sought to assess the course of HRQoL in children with epilepsy over the first two years after diagnosis of epilepsy, and to assess the risk and protective factors for HRQoL. The second phase followed up with the initial cohort at approximately 8 and 10 years after diagnosis to examine the long-term course of HRQoL and associated child and family characteristics. Each phase of HERQULES was funded by a Canadian Institutes of Health Research Operating Grant (MOP-63411 and MOP-115015).

Beginning in 2004, all practicing paediatric neurologists treating children with epilepsy across Canada were invited to participate in the study. A total of 72 neurologists were eligible, and 53 (74%) agreed to participate. These neurologists were asked to inform the parents or caregivers of all consecutive patients who met the study inclusion criteria about the study over a 36-month period. Patients were considered to be eligible for the study if:

1. they were seen for the first time by a participating paediatric neurologist for epilepsy;
2. they were diagnosed between 4 and 12 years of age; and
3. their parent/caregiver who would be participating in the study had been the child's primary caregiver for at least the past six months.

Patients were ineligible for the study if they were diagnosed with other degenerative neurological disorders or major comorbid disorders likely to affect quality of life, or if their parent/caregiver (hereafter referred to as parents) did not have sufficient English language proficiency to complete the study questionnaires. It should be noted that the definition of a new case of epilepsy for inclusion in HERQULES during the recruitment phase was two or more unprovoked seizures >24h apart, typically used by clinicians and researchers at that time. The definition of epilepsy was updated by ILAE in 2014 to include special circumstances that do not meet the old definition (1).

Ethics approval for the first phase of the study was obtained from the research ethic boards governing each of the 17 participating paediatric neurologists' centers across Canada. For the second phase, ethics approval was only required from the Western University Health Science Research Ethics Board given that the research team had already established relationships with the participants to re-contact them directly (Western University Health Sciences Research Ethics Board file #10069E and #102819).

The first phase of HERQULES followed the participants for approximately two years after diagnosis and collected data at four time points: baseline, 6 months, 1 year, and 2 years post-diagnosis. Parents were asked to complete mailed questionnaires at these four times. Parents were also asked to give consent for their paediatric neurologist to provide their child's clinical information to the study team. For each child whose parent consented, neurologists were asked to complete an assessment form to describe the clinical features of the child's epilepsy at the same four data collection times (Appendix A). A total of 455 eligible families were identified, 373 (82%) of whom were successfully recruited and 282 (76%) of whom were retained at the 2-year follow-up.

In the second phase of HERQULES, the families that completed the first phase were re-contacted and asked to participate in two additional assessments at approximately 8 and 10 years post-diagnosis. Self-report by AYAs was introduced in these two additional assessments, and AYAs were eligible to provide self-report if they were aged 11 years or older. A total of 220 AYAs were eligible to provide self-report at the beginning of the

second phase of HERQULES. Informed consent was again sought to contact the physician currently providing epilepsy care, if applicable, to obtain the AYAs' clinical information. Consent was sought from AYAs who were 18 years or older, from both the parents and AYAs 16-18 years of age, and from parents if the AYAs were younger than 16 years.

Both phases of HERQULES followed the Tailored Design Method to encourage participation and retention in the study. The technique has been shown to maximize response rates and data quality in survey research studies, and includes the use of systematic follow-up and reminders, annual contact by mail, and tokens of appreciation for participation (88). The Tailored Design Method was applied in the communications with the AYAs, the participating parents, and the paediatric neurologists.

4.2 Measures

Data from the baseline, 2-year, 8-year, and 10-year follow-up of HERQULES were used. Variables that were examined in this thesis are presented below in the order of exposure, outcome, potential mediator, and covariates.

4.2.1 Exposure: Epilepsy Severity

Neurologists rated the severity of the AYAs' epilepsy using the Global Assessment of Severity of Epilepsy (GASE) scale, a single-item, 7-point Likert scale developed for HERQULES (89). The GASE scale ranged from 1 (extremely severe) to 7 (not at all severe), with higher scores indicating less severe epilepsy. The scale allows clinicians to report on the overall severity of epilepsy, taking into consideration the multidimensional nature of epilepsy. The GASE scale has demonstrated adequate validity, reliability, and responsiveness (89,90). As the clinical management of epilepsy is often dynamic during the initial period following diagnosis, epilepsy severity was measured at the 2-year follow-up when the situation has more likely stabilized to allow the neurologists to make a more accurate categorization of the clinical characteristics of the AYAs' epilepsy

and attempt to determine whether the AYAs' seizures could be controlled by combinations of AEDs.

4.2.2 Outcome: Epilepsy Worry

Information regarding epilepsy worry was obtained from the AYAs at the 10-year follow-up. Epilepsy worry was measured using the QOLIE inventory—an instrument that measures HRQoL for people with epilepsy and contains a section for epilepsy worry. Two versions of QOLIE were used: QOLIE-31 for young adults (age 18+) and QOLIE-AD-48 for adolescents (age 11-17) (35,53). In the QOLIE-31, epilepsy worry is measured with a "seizure worry" subscale consisting of five items, measuring the frequency and intensity of seizure-related worry (Table 4.1). Epilepsy worry is not a subscale in QOLIE-AD-48. Instead, three items, two of which are analogous to the items in QOLIE-31, are included as optional items (Table 4.2). AYAs given the QOLIE-AD-48 were able to choose not to respond to these three items. The three items measure the frequency of seizure-related fear or worry over the past four weeks using a 5-point scale, with higher scores indicating lower frequency (1: Very often; 5: Never).

Table 4.1: Epilepsy worry items in QOLIE-31 (designed for young adults aged 18+).

* Have you worried about having another seizure? (1 = All of the time … 6 = None of the time)
How fearful are you of having a seizure during the next month? (1 = Very fearful … 4 = Not fearful at all)
* Do you worry about hurting yourself during a seizure? (1 = Worry a lot 2 = Occasionally worry 3 = Don't worry at all)
How worried are you about embarrassment or other social problems resulting from having a seizure during the next month? (1 = Very worried … 4 = Not worried at all)
For each of these PROBLEMS, circle one number for how much they bother you 1. Seizures (1 = Not at all bothersome … 5 = Extremely bothersome)

*common items between QOLIE-31 and QOLIE-AD-48 selected to combine the two age groups.

Table 4.2: Epilepsy worry items in QOLIE-AD-48 (designed for adolescents aged 11-17).

In the past 4 weeks, how often did you:
* Worry about having another seizure? (1 = Very often … 5 = Never)
Fear dying because of seizures? (1 = Very often … 5 = Never)
* Worry about hurting yourself during a seizure? (1 = Very often … 5 = Never)

*common items between QOLIE-31 and QOLIE-AD-48 selected to combine the two age groups.

Both versions of QOLIE have been assessed for their psychometric properties. The QOLIE-31 has been shown to have good discriminant validity in terms of the differences in seizure frequency and severity categories (35). QOLIE-31 has also demonstrated acceptable internal consistency (Cronbach's α = 0.77-0.85) and test-retest reliability (Pearson's *r* = 0.64-0.85), with the seizure worry subscale scores of Cronbach's α = 0.79 and Pearson's *r* = 0.84 (35). The QOLIE-AD-48 has also demonstrated good construct validity, internal consistency, and test-retest reliability (53); however, the epilepsy worry items used for the purposes of this thesis were optional items and were not included as a part of any subscale or the summary score for the instrument, and therefore were not included in these assessments. Although these items in QOLIE-AD-48 were not validated and cover fewer aspects of epilepsy worry compared to the seizure worry subscale in QOLIE-31, they still capture the main concerns of epilepsy worry, specifically worry about having another seizure and worry about injuries from seizure, which this thesis is interested in. These items are also sensitive to change in levels of epilepsy worry by employing the Likert scale, instead of a yes/no question. These items from the QOLIE-AD-48 have demonstrated good internal consistency in the HERQULES sample of AYAs, with Cronbach's α = 0.86.

In order to analyze the whole sample together and not lose statistical power, the two items that were common between QOLIE-31 and QOLIE-AD-48 (worry about having another seizure and worry about injuries from seizure) were selected to be used.

Following the scoring scheme of QOLIE-31 (91), the two individual items were first converted to a score of 0-100, then added together and divided by 2 to generate an epilepsy worry score of 0-100. For this score, higher values indicate less epilepsy worry, due to the direction of the response options. Thus, the scores were subtracted from 100 to generate an epilepsy worry score of 0-100 where higher values indicate higher levels of epilepsy worry. The scores were dichotomized into whether epilepsy worry was absent or present (0 vs 1-100), and the frequency from the two sub-groups of younger and older participants was combined. For evaluating the level of epilepsy worry when it is present, Z-scores for the two sub-groups were calculated among those who experienced epilepsy worry, and the resulting Z-scores from the two sub-groups were combined.

4.2.3 Potential Mediator: Parents' Worry

Information regarding parents' worry was obtained from the Child Health Questionnaire – Parent Form (CHQ-PF50), a parent-report measure evaluating HRQoL for children and adolescents aged 5 to 18 years (92). Parents' worry was obtained at the 8-year follow-up to allow for a reasonable temporal sequence between exposure (epilepsy severity), mediator (parents' worry), and outcome (epilepsy worry). The CHQ contains 13 health concepts: nine are HRQoL concepts focusing on the child, while the remaining four concepts measure the impact on the family. The questions used to evaluate parents' worry in this thesis were derived from the "parental impact – emotional" concept from the CHQ. This concept examines the levels of worry the parent experienced over the past 4 weeks regarding three aspects of their child's health: physical health, emotional well-being or behaviour, and attention or learning abilities (Table 4.3). Each of the three aspects is scored on a 5-point scale, from "none at all" to "a lot". The CHQ provides scoring for each individual concept in the measure (92). The "parent impact-emotional" subscale scoring ranges from 0-100, with higher scores indicating lower levels of parents' worry. The subscale has acceptable internal consistency within the HERQULES sample of AYAs, with Cronbach's $\alpha = 0.80$.

Table 4.3: "Parental impact – emotional" concept from CHQ-PF50.

During the past 4 weeks, how much emotional worry or concern did each of the following cause you?
a. Your son's/daughter's physical health (None at all – A little bit – Some – Quite a bit – A lot)
b. Your son's/daughter's emotional well-being or behaviour (None at all – A little bit – Some – Quite a bit – A lot)
c. Your son's/daughter's attention or learning abilities (None at all – A little bit – Some – Quite a bit – A lot)

4.2.4 Covariates: Adolescents and Young Adults

Anxiety

Assessments of anxiety were obtained from AYAs' self-report at the 10-year follow-up. Anxiety was measured using the Spielberger State-Trait Anxiety Inventory short-form (STAI: Y-6) (93) (Appendix B). The 6-item inventory measures a person's current level of anxiety with a 4-point scale and has a total score range of 20 to 80 with higher scores indicating higher anxiety. The inventory has been shown to have good validity and reliability (93). The inventory has acceptable internal consistency within the HERQULES sample of AYAs, with Cronbach's $\alpha = 0.87$.

Depression

Assessments of depression were obtained from AYAs' self-report at the 10-year follow-up. Depression was measured using the Centre for Epidemiological Studies Depression Scale (CES-D), an instrument that has been validated and is frequently used in general population surveys (94) (Appendix B). The CES-D is a 20-item self-reported scale that measures depressive symptoms over the past 4 weeks using a 4-point scale. The total score for CES-D ranges from 0 to 60 with higher scores indicating greater depressive

symptoms. A score of 16 or greater is indicative of clinically relevant depression (94). The CES-D has been found to have good psychometric properties in the general population (94). The instrument has acceptable internal consistency within the HERQULES sample of AYAs, with Cronbach's α = 0.92.

AYAs' age

AYAs' age at the 10-year follow-up was determined by computing the time between the completion date of the AYAs' 10-year follow-up questionnaire and the AYAs' date of birth.

AYAs' sex

AYAs' sex (male or female) was reported by their parents at baseline.

Recency of last seizure

At the 10-year follow-up, AYAs were asked to indicate when their last seizure was, or to provide a best guess if they were not sure. The response 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. For AYAs who could not recall or did not report on the recency of their last seizure, their parents' reported value on the same question was imputed. Due to the unequal time intervals between the individual response options, this variable was dichotomized into whether or not the AYA had achieved 5-year seizure freedom at the 10-year follow-up.

Current use of AEDs

At the 10-year follow-up, AYAs were asked "Are you currently taking any medication(s) to treat epilepsy or seizures?". The response options were "yes" and "no". For those who reported that they were not currently taking medications for their epilepsy or seizures, they were asked "When was the last time you took medication for epilepsy or

seizures?" The response options were: less than 6 months ago; 6 months to less than 1 year ago; 1 year to less than 2 years ago; more than 2 years ago; I have never taken medication(s) for epilepsy or seizures; I don't remember.

Seizure type

Neurologists reported on AYAs' epilepsy syndrome as well as seizure type based on the ILAE's classifications (primary generalized, absence, simple/complex partial, benign epilepsy of childhood with rolandic spikes (BECRS), secondarily generalized, BECRS + secondarily generalized, or undetermined) (95,96). These data were then used to create a more general category of the AYAs' seizure type (generalized, partial, or undetermined). Data regarding seizure type were taken from the same 2-year follow-up time as the exposure of interest (epilepsy severity).

Behavioural comorbidities

At the 2-year follow-up, neurologists were asked "Does the patient have behavioural problems?" and the response options were "no (normal)" and "yes". If the response was "yes", the neurologists were also asked to report on the severity (mild, moderate, or severe) of the behavioural problems and the diagnosis (if any). The data collected were combined into a dichotomous variable of "yes" and "no".

Cognitive comorbidities

At the 2-year follow-up, neurologists were asked "Does the patient have cognitive problems?" and the response options were "no (normal)" and "yes". If the response was "yes", the neurologists were also asked to report on the severity (borderline, mild, moderate, or severe) of the cognitive problems and the diagnosis (if any). The data collected were combined into a dichotomous variable of "yes" and "no".

4.2.5 Covariates: Parents and Families

Parents' age

Parents' age at the 10-year follow-up was determined by computing the time between the date of completion of the questionnaire and the parents' date of birth.

Parents' depressive symptoms

Parents' depressive symptoms were assessed at the 10-year follow-up, using the same CES-D scale as used in the AYA self-reports as described earlier (94). The instrument has a good internal consistency within the sample of AYAs' parents, with Cronbach's α = 0.91.

Parents' marital status

Parents reported on their marital status (married, widowed, divorced, separated, remarried, never married) at the 10-year follow-up. The categories were collapsed to create a binary variable indicating whether parents were currently married (married, remarried) or not (widowed, divorced, separated, never married).

Family income

Parents were asked to report their yearly household income before taxes at the 10-year follow-up. The response options ranged from less than $20,000 to greater than $150,000. These categories were collapsed into fewer categories (less than $50,000, $50,000 to $99,999, $100,000 - $149,000, greater than $150,000) for analysis to account for low cell counts in some of the response categories.

Family resources

Level of family resources at the 10-year follow-up was assessed using the Family Inventory of Resources for Management (FIRM), a self-report instrument using a 4-point Likert scale for assessing the extent to which resources are available for families to

adapt to stressful life events (97). The FIRM contains four subscales, two of which (Family Strength: Mastery and Health (20 items), Extended Family Support (4 items)) have been found to be associated with adaptation to childhood epilepsy and were selected for use in HERQULES (98) (Appendix C). The scoring ranges from 0 to 72, with higher scores indicating more resources. The instrument has been found to have acceptable validity and reliability (Family Strength: Mastery and Health subscale: Cronbach's α = 0.85, Extended Family Support subscale: Cronbach's α = 0.62) (97). The instrument has acceptable internal consistency in our sample, with Cronbach's α = 0.93 for the Family Strength: Mastery and Health subscale and Cronbach's α = 0.83 for the Extended Family Support subscale.

Family demands

Family demands at the 10-year follow-up were assessed using the Family Inventory of Life Events & Changes (FILE), a 71-item self-report measure of family stress in the previous year across 9 domains (97) (Appendix C). The FILE accounts for both normative and non-normative life events experienced by the family, and scores can be obtained for each domain as well as a total “pile up” scale. The FILE score ranges from 0 to 71, with higher scores indicating more family stress in the previous year. The FILE has demonstrated acceptable discriminant validity, internal consistency (Cronbach's α = 0.72), and test-retest reliability (Pearson’s *r* = 0.80) (97). The instrument has acceptable internal consistency in our sample (Cronbach's α = 0.81).

Family adaptation

Family adaptation at the 10-year follow-up was measured using the Family Adaptability, Partnership, Growth, Affection and Resolve (APGAR) (99) (Appendix C). The instrument has five items scored using a 5-point Likert scale, and the total score ranges from 0 to 20 where higher scores indicate higher satisfaction with family functioning. The APGAR has been found to be both valid and reliable (99–101). The instrument has acceptable internal consistency in our sample, with Cronbach's α = 0.90.

4.3 Statistical Analysis

All analyses were conducted using Stata/MP 13.0 for Mac (StataCorp, College Station, TX, USA).

4.3.1 Sample Characteristics

Summary statistics were used to describe the clinical, demographic, and family characteristics of the sample. Means and standard deviations were reported for continuous variables, and frequencies and proportions were reported for categorical variables.

4.3.2 Analysis for Objective #1

Objective #1: To describe the extent to which AYAs with childhood-onset epilepsy experience epilepsy worry, and to explore its associations with epilepsy severity and other clinical, demographic, and family characteristics.

The presence or absence of epilepsy worry was summarized using frequencies and proportions. The epilepsy worry scores among those who experienced epilepsy worry were standardized and summarized using a histogram of the score distribution. Bivariate analyses were conducted to assess the associations of the presence and level of epilepsy worry with epilepsy severity, other clinical epilepsy characteristics, demographic, and family characteristics, without controlling for other factors. The factors assessed included: AYA age, AYA sex, recency of last seizure, current use of AEDs, seizure type, behavioural comorbidities, cognitive comorbidities, parents' age, parents' depressive symptoms, parents' marital status, family income, family resources, family demands, and family adaptation.

Multivariable analyses were conducted to assess the relationship between epilepsy worry and epilepsy severity and other clinical, demographic, and family characteristics. A preliminary analysis revealed that there was a large number of zeros in the epilepsy worry scores, suggesting that the majority of AYAs did not experience epilepsy worry.

Zero-inflated and hurdle models are commonly considered when the outcome of interest include excess zeros. Zero-inflated models contain zeros arising from two different processes: from at-risk and not-at-risk populations in public health perspectives, while hurdle models only contain zeros arising from one at-risk population (102). For the purposes of this thesis, all AYAs in the sample have childhood-onset epilepsy and were at risk of experiencing epilepsy worry. As such, the hurdle model was chosen over the zero-inflated model. A logistic regression was first performed with the outcome being presence or absence of epilepsy worry, which represents the "hurdle" to be crossed in the hurdle model. Odds ratios from the logistic regression were reported for this portion of the model. After the hurdle is crossed, the level of epilepsy worry among the AYAs who did experience epilepsy worry was modelled using the gamma distribution due to the epilepsy worry scores being continuous and highly positively skewed. Mean ratios were reported for this portion of the model.

4.3.3 Analysis for Objective #2

Objective #2: To explore the extent to which epilepsy worry correlates with anxiety and depression in AYAs with childhood-onset epilepsy.

The hurdle model approach was also applied to examine the extent to which epilepsy worry correlates with anxiety and with depression. The correlations between the presence or absence of epilepsy worry and anxiety and between the presence or absence of epilepsy worry and depression were evaluated using point-biserial correlation, which is mathematically equivalent to the Pearson correlation. The correlations between the level of epilepsy worry and anxiety and between the level of epilepsy worry and depression among the AYAs who experienced epilepsy worry were evaluated using Pearson correlation. The correlation between anxiety and depression was also examined using Pearson correlation.

4.3.4 Analysis for Objective #3

Objective #3: To explore the extent to which parents of AYAs with childhood-onset epilepsy experience worries regarding their child's health, and whether it mediates the effect of epilepsy severity on AYAs' epilepsy worry.

Parents' worry score was summarized using sample mean, standard deviation, range, and sample distribution. Mediation was examined using the Baron and Kenny method, which suggests the following steps for establishing mediation (103):

1. Assess the association between the exposure (epilepsy severity) and the outcome (epilepsy worry);
2. Assess the association between the exposure (epilepsy severity) and the potential mediator (parents' worry); and
3. Assess the association between the potential mediator (parents' worry) and the outcome (epilepsy worry), adjusting for the exposure (epilepsy severity).

Baron and Kenny suggest that all three steps should be met in order to establish mediation (103). However, several authors have argued that a significant association in step one is not required to establish mediation, as the requirement would rule out the possibility of a suppression effect in which the indirect effect and the direct effect have opposite directions and may cancel out (104–106). Given this, the subsequent steps were performed regardless of the significance of the association assessed in step one.

The mediation analyses were also performed using the binomial-gamma hurdle model. Each association was first assessed with the outcome being the presence or absence of epilepsy worry, and assessed again with the outcome being the level of epilepsy worry among those who experienced epilepsy worry.

4.3.5 Attrition Analysis

To assess the potential for attrition bias, characteristics of families that completed baseline and 10-year follow-up questionnaires were compared to those of families that completed baseline but not 10-year follow-up questionnaires. Characteristics that were

included in the attrition analysis were: child age, child sex, epilepsy severity, seizure type, behavioural problems, cognitive problems, parents' age, parents' depressive symptoms, parents' worry, parents' marital status, family income, family resources, family demands, and family adaptation. T-tests were used to compare continuous variables and chi-square tests/fisher's exact tests were used to compare proportions for categorical variables.

4.3.6 Missing Data

Complete data were available for about 70% of the sample. A comparison of AYAs who had complete data versus those who did not have complete data was made to assess whether the characteristics of the two groups differed significantly (Appendix D). The proportion of missing data for each individual variable of interest is shown in Table 4.4. Most of the missing data were in demographic variables from questionnaires that were not returned at the 10-year follow-up, or in AYAs' clinical characteristics due to missing paediatric neurologist reports at the 2-year follow-up. A complete-case analysis would exclude over 25% of participants, yielding potentially biased and inefficient results. Multiple imputation (107) was used to address missing data in this thesis. In particular, the multiple imputation by chained equations (MICE) method was adopted for its flexibility to accommodate arbitrary missing patterns and use a separate conditional distribution for each imputed variable (108). Specifically, using the MICE method, one can use logistic regression models to impute categorical data, and linear regression models to impute continuous data. One can also impute data using MICE through the predictive mean matching method, which fills a missing value by matching the missing value with the closest predictive mean (109). The advantage of predictive mean matching is that the imputed values are guaranteed to be consistent with the observed values, as the method samples values form the observed data. This method is less sensitive to violations of model assumptions compared to imputation by parametric regression (110). All variables involved in the analysis were used for the imputation to maintain congeniality between the imputation models and the analysis models. To

perform multiple imputation, the missing data were filled in *m* times with estimated values, creating *m* complete data sets. Each of the imputed data sets were then analyzed using the desired statistical method, and the estimates from each analyzed data set were combined using Rubin's rule (107) to produce a single set of results. To reduce the sampling error from imputations and prevent loss of statistical power, 20 imputations were made based on the recommendations of Graham and colleagues for 10% to 30% of missing data (111).

Table 4.4: Proportion of missing data for each variable of interest.

Variable	**% missing**
AYA-report	
AYA age	0
5-year seizure freedom	0.8
AED use	2.3
Neurologist-report	
Epilepsy severity	9.2
Seizure type	13.8
Behaviour comorbidities	8.5
Cognitive comorbidities	9.2
Parent-report	
AYA sex	0
Parents' age	7.7
Parents' worry	3.8
Parents' depressive symptoms	7.7
Parents' marital status	7.7
Family income	8.5
Family resources	7.7
Family demands	7.7
Family adaptation	7.7

AYA, adolescent and young adult; AED, anti-epileptic drug.

Chapter 5

5 Results

This chapter presents the findings of this thesis. The sample characteristics are first described in section 5.1, followed by results of attrition analysis in section 5.2. The last three sections (sections 5.3 – 5.5) present the results for each research objective.

5.1 Sample Characteristics

At the 10-year follow-up, 176 questionnaires were sent to AYAs, and 131 returned completed questionnaires. One AYA did not report on the outcome of interest (epilepsy worry) and was excluded from the study. The characteristics of the 130 AYAs included in the study are summarized in Table 5.1. The AYAs were on average 17.8 years old (SD = 2.6) and the age ranged from 12 to 23 years old. The proportions of males and females in this sample were similar, with 47.7% male and 52.3% female. The majority (82.4%) of the AYAs were still going to school at the 10-year follow-up. In terms of their current epilepsy status, the majority (63.1%) of AYAs had been seizure-free for at least five years, and about 14.0% of AYAs had experienced seizures within the last year. About three quarters of the AYAs (73.2%) reported that they were no longer taking AEDs. The majority (65.4%) of the AYAs were no longer receiving care for their epilepsy or seizures at the 10-year follow-up, whereas 26.0% of the AYAs continued to receive care for their epilepsy or seizures from either an adult neurologist, paediatric neurologist, or family doctor/general practitioner.

Of the 130 AYAs included in the study, 119 of their paediatric neurologists provided information about the AYAs' clinical characteristics at the 2-year follow-up. These characteristics are summarized in Table 5.2. For most of the AYAs, their epilepsy severity was either "not at all severe" (60.2%) or "a little severe" (24.6%) two years after their epilepsy diagnosis. The seizure type at the same time point was generalized for 40.2% of AYAs and partial for 56.3% of AYAs. In terms of comorbidities, 14.3% of AYAs had behavioural problems and 20.2% had cognitive problems at the 2-year follow-up.

The characteristics of the parents of AYAs at the 10-year follow-up are summarized in Table 5.3. Of the 130 AYAs included in the study, 120 of their parents returned completed questionnaires at the 10-year follow-up. The majority (90%) of these parents were the AYAs' biological mothers. These parents were on average 48.8 years old (SD = 5.2) at the 10-year follow-up and the majority (82.5%) were currently married with 2.5% being remarried. These parents scored an average of 10.1 (SD = 8.9) on the CES-D scale, with 22.5% having clinically significant depressive symptoms. The AYAs' family characteristics at the 10-year follow-up are also presented in Table 5.3. About half (50.4%) of the families had an annual household income of $100,000 or greater. On average, the families had adequate resources (FIRM = 51.7, SD = 11.9), reported low levels of stress (FILE = 8.4, SD = 5.9), and were functioning well (APGAR = 14.6, SD = 4.0).

5.2 Attrition Analysis

Figures 5.1 and 5.2 present the timeline for HERQULES and the number of participants at each data collection time point. At baseline, a total of 373 families participated in the study. AYA self-report was added for the second phase of the study at 8 and 10 years post-diagnosis. At the 10-year follow-up, 131 AYAs returned completed questionnaires. Table 5.4 presents the results of attrition analysis comparing the baseline characteristics between families who participated in the 10-year follow-up and were included in the current study (n = 130) with those who were lost to follow-up (n = 243). The two groups were similar in terms of AYAs' sex, age, epilepsy severity, seizure type, parents' marital status, and family adaptation. However, AYAs who were lost to follow-up were more likely to have behavioural or cognitive problems at the time of epilepsy diagnosis. The families lost to follow-up had lower household income, fewer family resources, and more family stress in the previous year, and the parents in these families were on average younger and experienced more depressive symptoms and more worry regarding their child's health at baseline.

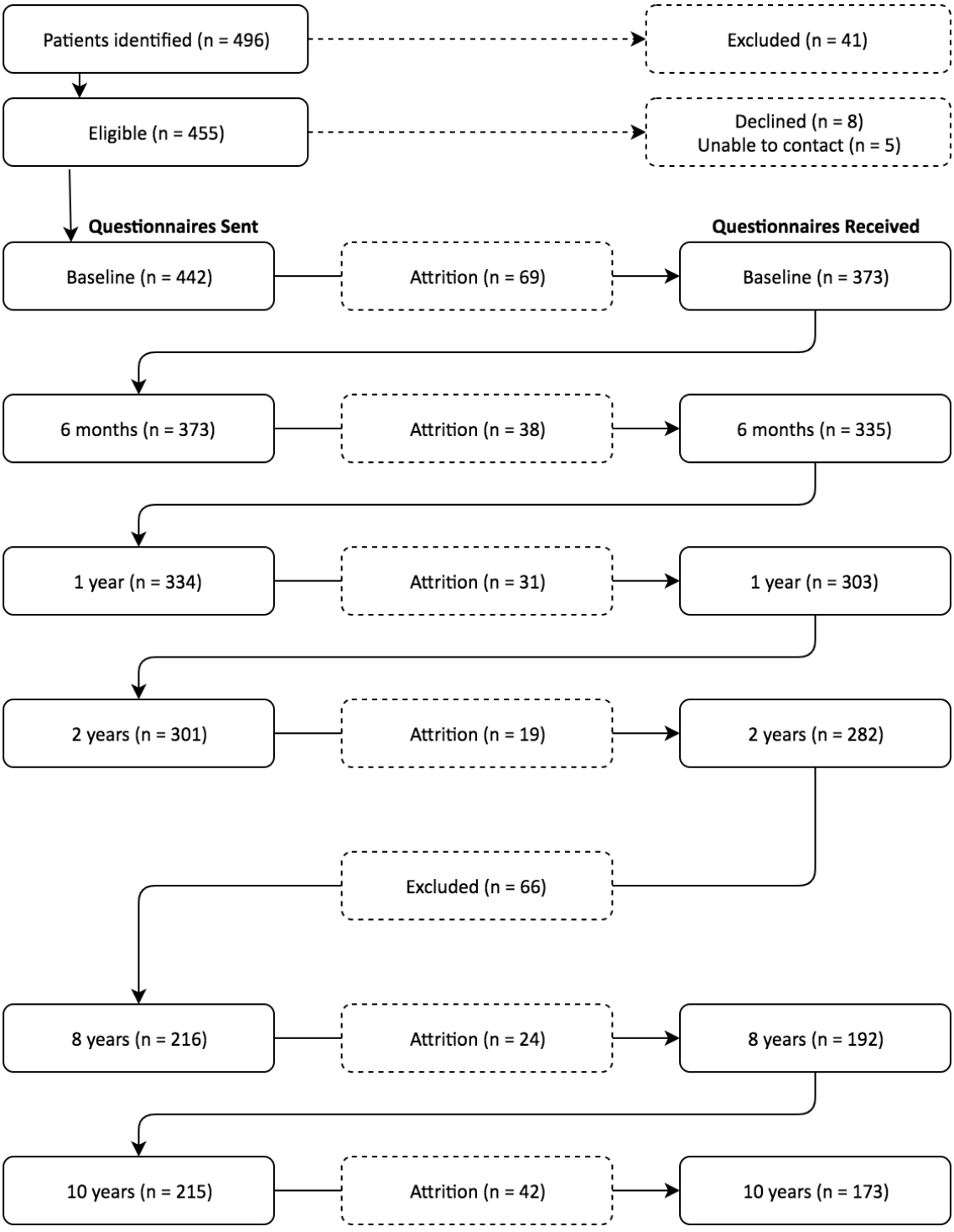

Figure 5.1: HERQULES participant flow diagram (parent/family).

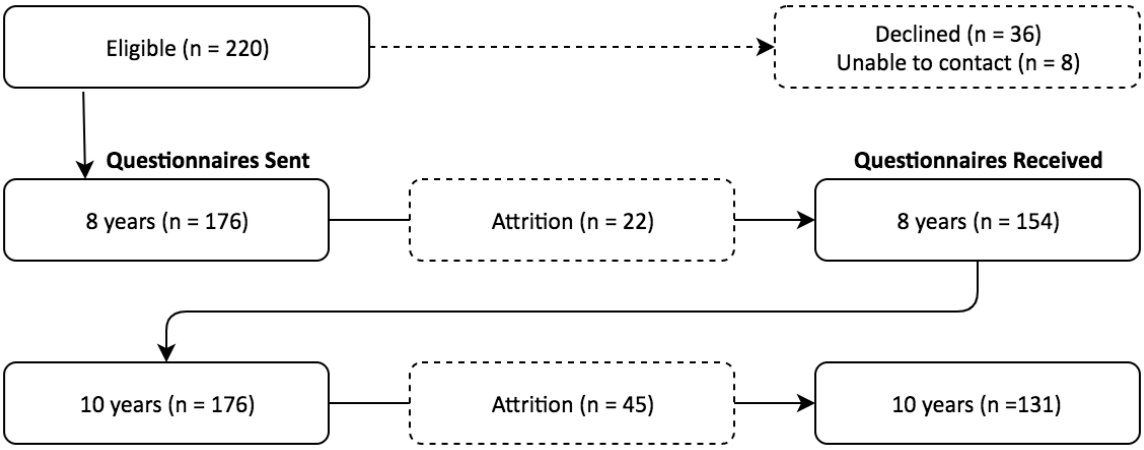

Figure 5.2: HERQULES participant flow diagram (AYA).

5.3 Results for Objective #1

Objective #1: To describe the extent to which AYAs with childhood-onset epilepsy experience epilepsy worry, and to explore its associations with epilepsy severity and other clinical, demographic, and family characteristics.

At the 10-year follow-up, 80 (61.5%) AYAs had not experienced any epilepsy worry within the past four weeks, while 50 (38.5%) AYAs had experienced at least some epilepsy worry. Among these 50 AYAs experiencing some epilepsy worry, 18 (36%) had achieved 5-year seizure freedom, while 32 (64%) had not. The epilepsy worry scores for these 50 AYAs were standardized and the distribution is shown in Figure 5.3. The distribution of epilepsy worry scores was highly skewed to the right with a skewness of 1.0. Considering epilepsy worry based on remission status, 22% of AYAs who have achieved 5-year seizure freedom experienced epilepsy worry, while 70% of AYAs who have not achieved 5-year seizure freedom experienced seizure worry.

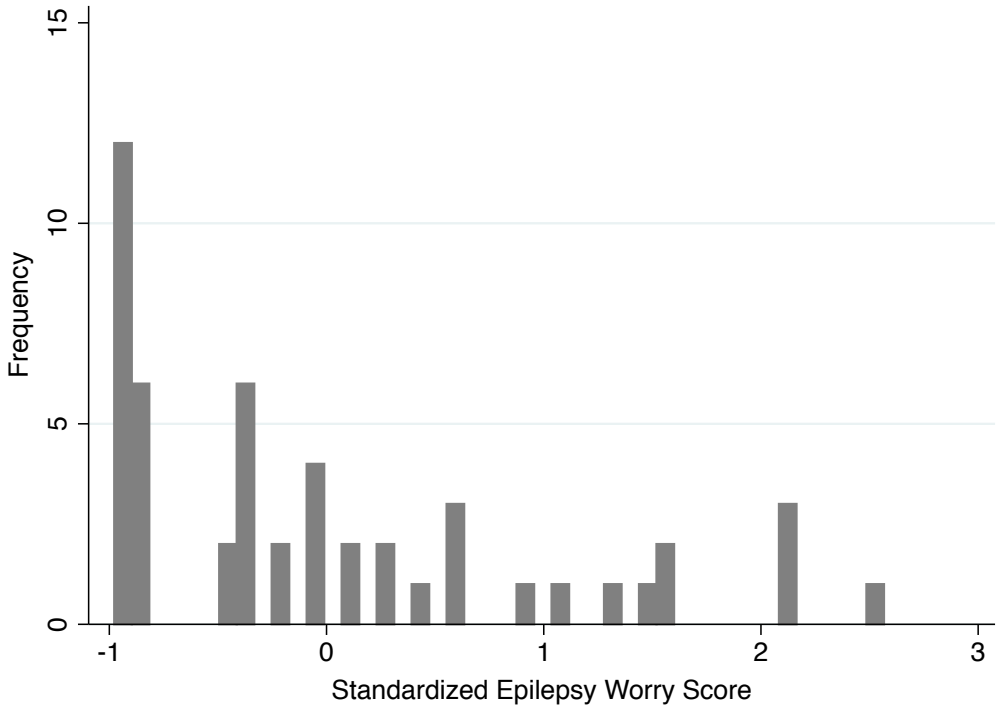

Figure 5.3: Distribution of standardized epilepsy worry score for AYAs who experienced epilepsy worry at the 10-year follow-up.

Table 5.5 summarizes the results of the bivariate analyses. AYAs who were female (OR = 2.50, 95% CI: 1.20, 5.20), older (OR = 1.18, 95% CI: 1.02, 1.36), and who were currently treated by AEDs (OR = 9.58, 95% CI: 1.34, 3.17) have higher odds of experiencing epilepsy worry, while having achieved 5-year seizure freedom (OR = 0.14, 95% CI: 0.06, 0.30) and lower epilepsy severity (OR = 0.58, 95% CI: 0.38, 0.87) were associated with lower odds of experiencing epilepsy worry. Of the family variables, AYAs who were in families that had more resources (OR = 0.96, 95% CI: 0.93, 1.00) and better functioning (OR = 0.90, 95% CI: 0.81, 0.98) have lower odds of experiencing epilepsy worry. Among AYAs who did experience epilepsy worry, having achieved 5-year seizure freedom was significantly associated with a 0.31 times reduction (95% CI: 0.18, 0.53) in the levels of epilepsy worry, while current use of AEDs was significantly associated with 4.18 times increase (95% CI: 2.61, 6.70) in the levels of epilepsy worry.

Table 5.6 summarizes the results of the multivariable analyses. Of the variables included in the models, only 5-year seizure freedom (OR = 0.26, 95% CI: 0.08, 0.89) and current use of AEDs (OR = 4.52, 95% CI: 1.12, 18.32) were significantly associated with the odds of experiencing epilepsy worry, and only current use of AEDs (MR = 5.37, 95% CI: 1.94, 14.84) was associated with the level of epilepsy worry. Epilepsy severity was neither associated with the odds of experiencing epilepsy worry (OR = 0.87, 95% CI: 0.51, 1.50) nor the level of epilepsy worry (MR =1.01, 95% CI: 0.78, 1.32).

5.4 Results for Objective #2

Objective #2: To explore the extent to which epilepsy worry correlates with anxiety and depression in AYAs with childhood-onset epilepsy.

The correlations between AYA epilepsy worry and anxiety and between AYA epilepsy worry and depression were assessed using point-biserial correlation and Pearson correlation. Complete-case analysis was conducted, as complete data were available for both epilepsy worry and depression, and only 3 out of 130 (2.3%) values in anxiety were missing. AYA anxiety had a weak positive correlation with the presence ($r = 0.28$, $p < 0.05$) and the level ($r = 0.14$, $p > 0.05$) of epilepsy worry. AYA depression had a moderate positive correlation with the presence ($r = 0.41$, $p < 0.05$) and the level ($r = 0.52$, $p < 0.05$) of epilepsy worry. Lastly, a strong positive correlation was found between anxiety and depression ($r = 0.76$, $p < 0.05$).

5.5 Results for Objective #3

Objective #3: To explore the extent to which parents of AYAs with childhood-onset epilepsy experience worries regarding their child's health, and whether it mediates the effect of epilepsy severity on AYAs' epilepsy worry.

The distribution of the parents' worry scores is presented in Figure 5.4. At the 8-year follow-up, the parents had a mean score of 69.5 (SD = 26.3) on the parental impact – emotional subscale. The scores ranged from 0 to 100, and 50% of the parents scored at

or above 75. Bivariate analysis with epilepsy worry indicated that parents' worry at the 8-year follow-up was not significantly associated with the odds of experiencing epilepsy worry in AYAs at the 10-year follow-up (OR = 1.00, 95% CI: 0.98, 1.01). On the other hand, higher scores on the parental impact – emotional subscale score, which is indicative of less parents' worry, were significantly associated with lower levels of epilepsy worry, with 1 unit increase on the parental impact – emotional subscale score being associated with 0.99 times reduction in the epilepsy worry score (95% CI: 0.98, 1.00).

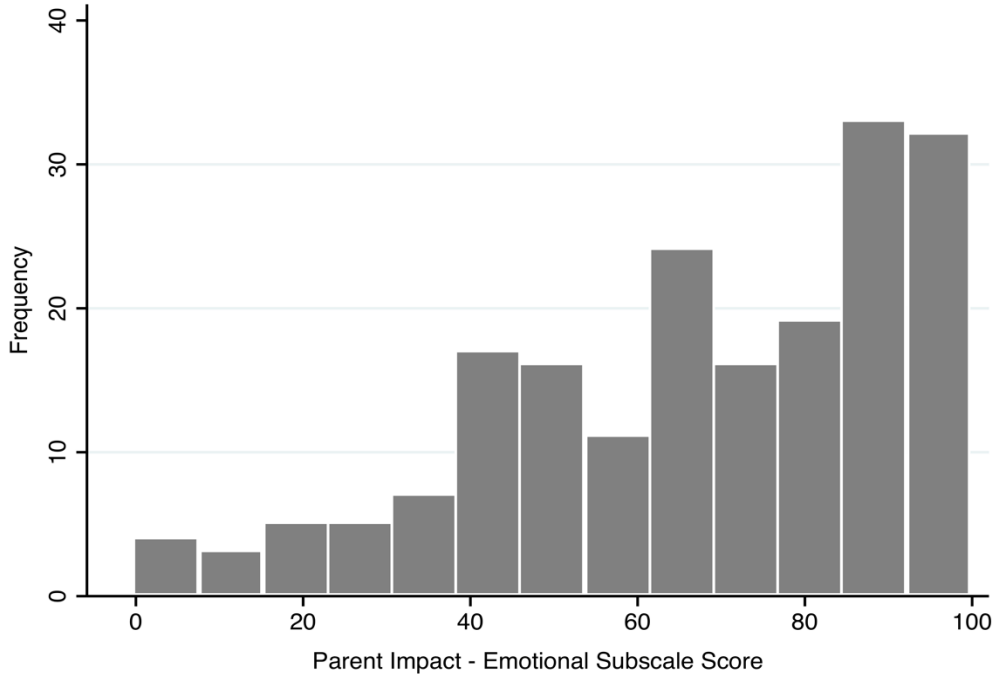

Figure 5.4: Distribution of parents' scores on the parental impact – emotional subscale at the 8-year follow-up.

Mediation analysis was conducted to assess the mediating effect of parents' worry on the association between epilepsy severity and epilepsy worry, and the results are presented in Tables 5.7 and 5.8. The first step to establish mediation for the Baron and Kenny method was to assess the association between the exposure (epilepsy severity) and the outcome (epilepsy worry). The association with adjustments for covariates was examined in objective one, and epilepsy severity was neither associated with the odds

of experiencing epilepsy worry (OR = 0.87, 95% CI: 0.51, 1.50) nor the level of epilepsy worry (OR =1.01, 95% CI: 0.78, 1.32). The second step to establish mediation was to assess the association between the exposure (epilepsy severity) and the mediator (parents' worry), which was found to be not significant (β = 2.12, 95% CI: -2.43, 6.66) from the results of regression analysis. The third step to establish mediation was to assess the association between the mediator (parents' worry) and the outcome (epilepsy worry). Parents' worry was neither associated with the odds of AYAs' epilepsy worry (OR = 1.01, 95% CI: 0.99, 1.04) nor the level of epilepsy worry (MR = 0.99, 95% CI: 0.98, 1.00).

Table 5.1: AYA characteristics at the 10-year follow-up (n = 130).

AYA sex, n (%)		
Male	62	(47.7)
Female	68	(52.3)
AYA age, mean (SD), [range]	17.8	(2.6), [12-23]
Time since last seizure, n (%)		
Less than 6 months ago	14	(10.1)
6 months ago to less than 1 year ago	5	(3.9)
1 year ago to less than 2 years	7	(5.4)
2 years ago to less than 5 years ago	20	(15.5)
5 years ago to less than 10 years ago	60	(46.5)
10 years ago or more	22	(17.1)
Don't remember	1	(0.8)
Current used of AEDs, n (%)		
Yes	34	(26.8)
No	93	(73.2)
Time since last AED, n (%)		
Less than 6 months ago	2	(2.3)
6 months to less than 1 year ago	0	(0)
1 year to less than 2 years ago	2	(2.3)
More than 2 years ago	61	(68.5)
Never taken medication(s) for epilepsy or seizures	11	(12.4)
Don't remember	13	(14.6)
Current epilepsy care status, n (%)		
Transferred from a pediatric specialist to an adult neurologist and was still receiving care for epilepsy/seizures	18	(14.2)
Transferred from a pediatric specialist to an adult neurologist but was no longer receive care for epilepsy/seizures.	3	(2.4)
Receiving care from a pediatric specialist	10	(7.9)
Receiving care from a family doctor/general practitioner.	5	(3.9)
Was not receiving care for epilepsy/seizures from any doctors now.	80	(63.0)
None of the above	10	(7.9)

AYA, adolescent and young adult; AED, anti-epileptic drug.

Table 5.2: AYA clinical characteristics at the 2-year follow-up (n = 119).

Epilepsy severity, mean (SD)	6.3 (1.1)
Epilepsy severity, n (%)	
1 = Extremely severe	0 (0)
2 = Very severe	2 (1.7)
3 = Quite severe	2 (1.7)
4 = Moderately severe	6 (5.1)
5 = Somewhat severe	8 (6.8)
6 = A little severe	29 (24.6)
7 = Not at all severe	71 (60.2)
Seizure type, n (%)	
Generalized	45 (40.2)
Partial	63 (56.3)
Undetermined	4 (3.6)
Behaviour comorbidities, n (%)	
Yes	17 (14.3)
No	102 (85.7)
Cognitive comorbidities, n (%)	
Yes	24 (20.2)
No	94 (79.0)

AYA, adolescent and young adult.

Table 5.3: Parent and family characteristics at the 10-year follow-up (n = 120).

Parents' age, mean (SD)	48.8 (5.2)
Parents' depressive symptoms, mean (SD)	10.1 (8.9)
CES-D score ≥ 16, n (%)	27 (22.5)
CES-D score < 16, n (%)	93 (77.5)
Parents' marital status, n (%)	
Married	96 (80.0)
Widowed	1 (0.8)
Divorced	9 (7.5)
Seperated	7 (5.8)
Remarried	3 (2.5)
Never married	4 (3.3)
Family income, n (%)	
Less than $50,000	19 (16.0)
$50,000 - $99,999	38 (31.9)
$100,000 - $149,000	28 (23.5)
$150,000 or more	32 (26.9)
Don't know	2 (1.7)
Family resources, mean (SD)	51.7 (11.9)
Family demands, mean (SD)	8.4 (5.9)
Family adaptation, mean (SD)	14.6 (4.0)

CES-D, Centre for Epidemiological Studies Depression Scale.

Table 5.4: Attrition analysis (baseline characteristics).

Characteristics	Lost to follow-up (n = 243)	Completed follow-up (n = 130)	p-value
AYA sex, n (%)			
Male	133 (54.73)	62 (47.7)	0.20
Female	110 (45.27)	68 (52.3)	
AYA age, mean (SD)	7.37 (2.30)	7.63 (2.41)	0.30
Epilepsy severity, mean (SD)	5.32 (1.22)	5.56 (1.10)	0.07
Seizure type, n (%)			
Generalized	89 (36.63)	54 (41.54)	0.61
Partial	146 (60.08)	74 (56.92)	
Undetermined	5 (2.06)	2 (1.54)	
Behaviour comorbidities, n (%)			
Yes	44 (18.11)	12 (9.23)	0.01
No	196 (80.66)	117 (90.00)	
Cognitive comorbidities, n (%)			
Yes	65 (26.75)	9 (6.92)	<0.0001
No	174 (71.60)	121 (93.08)	
Parents' age, mean (SD)	37.07 (6.39)	38.85 (5.37)	0.007
Parents' depressive symptoms, mean (SD)	15.35 (10.60)	12.31 (9.48)	0.007
Parents' worry, mean (SD)	44.40 (28.25)	50.71 (26.62)	0.04
Parents' marital status, n (%)			
Currently married	190 (78.19)	111 (85.38)	0.09
Not currently married	53 (21.81)	19 (14.62)	
Family income, n (%)			
Less than $50,000	60 (24.69)	18 (13.85)	0.02
$50,000 - $99,999	109 (44.86)	63 (48.46)	
$100,000 - $149,000	13 (5.35)	7 (5.38)	
$150,000 or more	43 (17.70)	37 (28.46)	
Family resources, mean (SD)	48.70 (11.12)	52.61 (10.76)	0.001
Family demands, mean (SD)	10.00 (6.92)	8.55 (5.61)	0.04
Family adaptation, mean (SD)	13.68 (3.66)	14.33 (3.89)	0.11

AYA, adolescent and young adult.

Table 5.5: Bivariate analysis of epilepsy worry with clinical, demographic, and family characteristics.

	Presence of epilepsy worry		Level of epilepsy worry	
Variable	**Odds ratio (SE)**	**95% CI**	**Mean ratio (SE)**	**95% CI**
AYA sex (ref = male)	2.50 (0.93)*	1.20, 5.20	0.88 (0.26)	0.49, 1.58
AYA age	1.18 (0.09)*	1.02, 1.36	1.08 (0.06)	0.97, 1.20
5-year seizure freedom (ref = no)	0.14 (0.06)*	0.06, 0.30	0.31 (0.09)*	0.18, 0.53
AED use (ref = no)	9.58 (4.44)*	3.86, 23.74	4.18 (1.01)*	2.61, 6.70
Epilepsy severity	0.58 (0.12)*	0.38, 0.87	0.88 (0.09)	0.72, 1.08
Seizure type (ref = generalized)	1.24 (0.42)	0.64, 2.41	0.92 (0.22)	0.57, 1.48
Behaviour comorbidities (ref = no)	0.91 (0.48)	0.33, 2.54	1.55 (0.63)	0.70, 3.45
Cognitive comorbidities (ref = no)	0.96 (0.44)	0.39, 2.37	0.91 (0.32)	0.46, 1.81
Parents' age	1.04 (0.04)	0.97, 1.12	1.00 (0.03)	0.95, 1.06
Parents' depressive symptoms	1.03 (0.02)	0.99, 1.08	1.01 (0.01)	0.98, 1.04
Parents' marital status (ref = not currently married)	0.57 (0.27)	0.22, 1.45	0.69 (0.24)	0.34, 1.38
Family income (ref = <50,000)	0.77 (0.14)	0.54, 1.11	1.06 (0.16)	0.79, 1.43
Family resources	0.96 (0.02)*	0.93, 1.00	0.98 (0.01)	0.95, 1.01
Family demands	1.03 (0.03)	0.97, 1.10	1.02 (0.03)	0.96, 1.07
Family adaptation	0.90 (0.04)*	0.81, 0.98	0.98 (0.04)	0.90, 1.07

AYA, adolescent and young adult; AED, anti-epileptic drug.

*$p < 0.05$

Table 5.6: Multivariable analysis of epilepsy worry with clinical, demographic, and family characteristics.

	Presence of epilepsy worry		Level of epilepsy worry	
Variable	**Odds ratio (SE)**	**95% CI**	**Mean ratio (SE)**	**95% CI**
Intercept	0.02 (0.07)	0.00, 33.42	0.16 (0.39)	0.00, 18.24
AYA sex (ref = male)	2.05 (1.04)	0.76, 5.54	0.57 (0.21)	0.28, 1.15
AYA age	1.07 (0.12)	0.86, 1.33	1.01 (0.08)	0.87, 1.17
5-year seizure freedom (ref = no)	0.26 (0.16)*	0.08, 0.89	0.90 (0.49)	0.31, 2.62
AED use (ref = no)	4.52 (3.23)*	1.12, 18.32	5.37 (2.79)*	1.94, 14.84
Epilepsy severity	0.87 (0.24)	0.51, 1.50	1.01 (0.14)	0.78, 1.32
Seizure type (ref = generalized)	1.52 (0.70)	0.61, 3.77	1.36 (0.39)	0.77, 2.38
Behaviour comorbidities (ref = no)	0.52 (0.43)	0.10, 2.67	1.02 (0.50)	0.39, 2.69
Cognitive comorbidities (ref = no)	1.09 (0.72)	0.30, 4.01	1.67 (0.73)	0.71, 3.95
Parents' age	1.04 (0.05)	0.94, 1.15	1.04 (0.04)	0.97, 1.12
Parents' depressive symptoms	1.02 (0.04)	0.94, 1.10	0.98 (0.02)	0.94, 1.02
Parents' marital status (ref = not currently married)	0.89 (0.61)	0.23, 3.44	0.87 (0.39)	0.36, 2.11
Family income (ref = <50,000)	0.79 (0.23)	0.45, 1.38	1.17 (0.19)	0.86, 1.60
Family resources	1.02 (0.04)	0.95, 1.10	0.99 (0.02)	0.95, 1.03
Family demands	1.00 (0.05)	0.90, 1.11	0.99 (0.04)	0.92, 1.06
Family adaptation	0.95 (0.07)	0.81, 1.11	0.95 (0.05)	0.86, 1.04

AYA, adolescent and young adult; AED, anti-epileptic drug.

*$p < 0.05$

Table 5.7: Analysis of parents' worry mediation effect (exposure → mediator).

Variable	Coefficient (SE)	95% CI
Intercept	3.52 (38.26)	-72.48, 79.52
AYA sex (ref = male)	-2.63 (4.94)	-12.43, 7.17
AYA age	0.88 (1.01)	-1.13, 2.89
5-year seizure freedom (ref = no)	16.32 (5.97)*	4.49, 28.15
AED use (ref = no)	6.35 (7.10)	-7.73, 20.43
Epilepsy severity	2.12 (2.29)	-2.43, 6.66
Seizure type (ref = generalized)	3.76 (4.17)	-4.52, 12.04
Behaviour comorbidities (ref = no)	3.10 (7.47)	-11.73, 17.93
Cognitive comorbidities (ref = no)	-17.73 (6.48)*	-30.61, -4.86
Parents' age	0.19 (0.47)	-0.74, 1.13
Parents' depressive symptoms	0.06 (0.46)	-0.85, 0.97
Parents' marital status (ref = not currently married)	1.38 (6.04)	-10.60, 13.37
Family income (ref = <50,000)	-4.37 (2.87)	-10.07, 1.33
Family resources	0.68 (0.34)*	0.01, 1.36
Family demands	-0.35 (0.53)	-1.40, 0.70
Family adaptation	-0.43 (0.74)	-1.90, 1.03

AYA, adolescent and young adult; AED, anti-epileptic drug.

*$p < 0.05$

Table 5.8: Analysis of parents' worry mediation effect (mediator → outcome).

	Presence of epilepsy worry		Level of epilepsy worry	
Variable	**Odds ratio (SE)**	**95% CI**	**Mean ratio (SE)**	**95% CI**
Intercept	0.02 (0.07)	0.00, 36.98	0.27 (0.64)	0.00, 27.87
Parents' worry	1.01 (0.01)	0.99, 1.04	0.99 (0.01)	0.98, 1.00
AYA sex (ref = male)	2.11 (1.08)	0.78, 5.76	0.54 (0.19)	0.27, 1.07
AYA age	1.06 (0.12)	0.85, 1.31	1.01 (0.07)	0.88, 1.16
5-year seizure freedom (ref = no)	0.21 (0.14)*	0.06, 0.77	1.05 (0.55)	0.38, 2.94
AED use (ref = no)	4.30 (3.09)*	1.05, 17.55	5.18 (2.55)*	1.97, 13.61
Epilepsy severity	0.85 (0.24)	0.49, 1.46	1.06 (0.14)	0.82, 1.37
Seizure type (ref = generalized)	1.47 (0.69)	0.59, 3.67	1.27 (0.36)	0.73, 2.20
Behaviour comorbidities (ref = no)	0.46 (0.40)	0.09, 2.51	1.16 (0.55)	0.46, 2.93
Cognitive comorbidities (ref = no)	1.49 (1.10)	0.35, 6.37	1.25 (0.57)	0.51, 3.06
Parents' age	1.04 (0.06)	0.94, 1.16	1.04 (0.04)	0.97, 1.11
Parents' depressive symptoms	1.02 (0.04)	0.94, 1.10	0.98 (0.02)	0.94, 1.02
Parents' marital status (ref = not currently married)	0.87 (0.60)	0.22, 3.34	0.98 (0.43)	0.42, 2.32
Family income (ref = <50,000)	0.82 (0.24)	0.46, 1.45	1.13 (0.17)	0.83, 1.53
Family resources	1.01 (0.04)	0.94, 1.09	1.00 (0.02)	0.96, 1.04
Family demands	1.00 (0.05)	0.91, 1.11	0.99 (0.03)	0.92, 1.05
Family adaptation	0.95 (0.08)	0.81, 1.11	0.94 (0.05)	0.85, 1.04

AYA, adolescent and young adult; AED, anti-epileptic drug.

*$p < 0.05$

Chapter 6

6 Discussion

This chapter discusses the findings of this thesis. Section 6.1 provides a summary of the findings by objective and the interpretation of the findings. Sections 6.2 and 6.3 discuss the strengths and limitations of this thesis. Section 6.4 proposes recommendations for future research, and section 6.5 concludes the chapter by discussing the implications of the study findings.

6.1 Summary of Findings

The purpose of this thesis was to explore the extent to which AYAs with childhood-onset epilepsy experience epilepsy worry 10 years after their epilepsy diagnosis, and to assess the relationship between epilepsy worry and AYAs' clinical, demographic, and family characteristics. In addition, this thesis examined the correlations between epilepsy worry, anxiety, and depression among AYAs, and assessed the potential mediating effect of parents' worry on their AYA's epilepsy worry.

6.1.1 Objective #1

The first objective of this thesis was to describe the extent to which AYAs with childhood-onset epilepsy experience epilepsy worry, and to explore its associations with epilepsy severity and other clinical, demographic, and family characteristics. Due to the unpredictable nature of seizures, people with epilepsy could experience a heightened sense of apprehension regarding the occurrence of future seizures and the related consequences, possibly even after seizure remission. In this study, it was found that nearly 40% of AYAs had experienced at least some epilepsy worry within the past four weeks at the 10-year follow-up. More than one-third of AYAs who had experienced epilepsy worry had achieved 5-year seizure freedom. When considering epilepsy worry based on remission status, about a fifth of AYAs who have achieved 5-year seizure freedom experienced epilepsy worry. The finding that AYAs continue to experience epilepsy worry after remission is consistent with what we expected, as well as with past

literature. In a study of the long-term psychological function in people with childhood-onset temporal lobe epilepsy 13 years after their first seizure, the authors found that 77% of the individuals in remission still experienced lingering worry about possible seizure recurrence (112). The higher proportion compared to our findings (77% vs 22%) may be due the differently defined seizure freedom status—the authors of this study defined seizure freedom as being free of seizures and AEDs for two or more years, whereas our study used 5-year seizure freedom as the cut-off point. The longer duration of seizure freedom in our study could allow AYAs more time to adjust to their remission status and outgrow their worry about epilepsy. Micallef and colleagues (112) also found that the proportion of people who were both experiencing epilepsy worry and were in remission was higher compared to those who had undergone epilepsy surgery and were either seizure-free or not, suggesting that the lingering epilepsy worry may be due to their spontaneous seizure remission not offering the same level of reassurance that their condition has been cured as compared to the surgical groups. This lack of reassurance may cause people to worry more about potential seizure recurrence and associated consequences like injuries and stigma. These findings offer some insights on addressing epilepsy worry—that psychological support should extend to those in seizure remission, and reassurance should be offered to those with spontaneous remission about the low probability of relapse to help with their psychological adjustment.

In the current study, we found that 5-year seizure freedom was associated with the AYAs' odds of experiencing epilepsy worry, but was not associated with the level of epilepsy worry after adjustments for other covariates. The finding that those with seizure freedom have lower odds of experiencing epilepsy worry is consistent with our expectation and findings from other studies. Micallef and colleagues (112) found similar results; a smaller proportion of people with childhood-onset temporal lobe epilepsy who had been seizure-free for two or more years experienced epilepsy worry, compared to those with ongoing seizures. In another study that prospectively followed children with epilepsy for 8 to 9 years after the initial epilepsy diagnosis, the authors found that having achieved 5-year seizure freedom at the follow-up was associated with a lower

risk of reporting internalizing problems, mainly depression and anxiety (113). This association is likely because AYAs who have been seizure-free for a long period of time are likely less or no longer affected by epilepsy in many domains of their lives, therefore are no longer worried about their condition and its impact. This interpretation is supported by other studies. One study found that adults with seizure freedom reported lower levels of illness intrusiveness and increased perceived control, self-esteem, and epilepsy specific QoL compared to those with ongoing seizures (114). Another study found that people who have longer duration of seizure remission have lower severity of subjective handicap, which the authors speculate could be reflective of increasing confidence that their epilepsy is resolved (115).

Our finding that 5-year seizure freedom was not associated with the level of epilepsy worry was unexpected. There are a few possible reasons for the insignificant association. First, this thesis examined 5-year seizure freedom as opposed to a more detailed measure of time since last seizure, such as in the works of O'Donoghue and colleagues (115). The possible association between duration of seizure remission and the level of epilepsy worry may have been lost with the dichotomization of the variable. Secondly, the subgroup that experienced epilepsy worry and was used for the analysis of the level of epilepsy worry had a small sample size—only 50 out of 130 AYAs in our sample experienced epilepsy worry at the 10-year follow-up. Although it is a positive outcome that the majority of AYAs did not experience epilepsy worry, the analysis may be underpowered to detect a significant effect due to the small sample size. Lastly, most AYAs in our sample have mild epilepsy severity or have outgrown their epilepsy, which continues to be the case when limiting attention to those experiencing epilepsy worry, and the distribution for the scores for epilepsy worry level was highly skewed to the right, suggesting that among AYAs who did experience epilepsy worry, the levels of epilepsy worry were low. As such, there may be insufficient variation in our data to detect an association.

This study also investigated the potential effects of AED use on epilepsy worry and found that AYAs who were currently using AEDs have higher odds of experiencing epilepsy worry and have higher levels of epilepsy worry. It is well recognized that various AEDs could initiate or worsen already existing behavioral or psychiatric problems. Many different AED options are available to treat epilepsy, and each option has its own possible adverse effects (33,116). For example, children with epilepsy who are being treated with levetiracetam have a higher risk of developing aggression, hostility, and nervousness compared to those who were on placebo (117). It is possible that for the AYAs who were currently using AEDs, the side-effects of AEDs may have altered their mood and thereby initiated or worsened their epilepsy worry. Unfortunately, HERQULES did not have data concerning the types of AED prescriptions that the AYAs were receiving, and the number of AYAs who were on AEDs at the 10-year follow-up (34 out of our sample of 130 AYAs) was too small to produce reliable results, especially when considering the many AED options available.

Another possible explanation for the association between AED treatment and epilepsy worry could be that the continuation of treatment is perceived as persisting epilepsy, even when the person has been seizure-free for some time. One study followed people with childhood-onset epilepsy for more than 30 years and found that those in remission but still taking AEDs have similar QoL compared to those not in remission, and both groups have significantly lower QoL scores compared to those in remission and discontinued AEDs (118). Both the behavioural and psychiatric side-effects of AEDs and the perception of lingering epilepsy that arose from continuing AED treatment could contribute to the lowered QoL, despite being in remission. Another study randomized people who had been in seizure remission for two years to either continue their AED treatment or slowly discontinue their AED treatment (119). This study found that those who discontinued AED treatment were less likely to worry about epilepsy or feel restricted by epilepsy than those with continued treatment, which is consistent with our results. The same study also found that people who discontinued AED treatment felt less internalized stigma and fewer restrictions on their social activities compared to

those with continued treatment, suggesting that the successful discontinuation of AEDs allow people with prior epilepsy to adopt the mindset that they have outgrown their epilepsy and are free from recurrent seizures and the stigma associated with epilepsy.

In our study, the hypothesized stressor, epilepsy severity two years after diagnosis, was not found to be associated with either the presence or the level of epilepsy worry 10 years after diagnosis in AYAs with childhood-onset epilepsy. Previous studies have examined epilepsy severity as a risk factor in children or adolescents with childhood-onset epilepsy and found that more severe epilepsy was associated with adverse outcomes such as poorer QoL (120), more emotional problems and depression (121), poorer self-esteem (122), and poorer emotional well-being (79). The finding of the insignificant association between epilepsy severity and epilepsy worry in this thesis could be due the overall mild epilepsy severity in the sample, even at two years post-diagnosis, and the mild severity may not have strongly affected the psychological development and well-being of these AYAs. This is supported by the findings from a review on the psychopathology and psychological adjustment in children and adolescents with epilepsy (121). The review found that epilepsy-related factors were significant risk factors for psychopathology in children with more severe epilepsy or poorer seizure control, but were not related to psychological and adaptation problems in children with less severe epilepsy or good seizure control.

Another possible explanation for the insignificant association between epilepsy severity and epilepsy worry is that an inadequate proxy may have been chosen to represent the stress and burden of a diagnosis of epilepsy and living with epilepsy. The variable chosen to represent the stress and burden was epilepsy severity two years post-diagnosis, which may not have adequately reflected the level of stress that the child and the family are required to take on with the child's epilepsy. For example, how well the child's seizures are controlled or how much the child's epilepsy severity has changed (either improved or worsened) over time could both contribute to the burden of living with epilepsy, but may not have been captured by the epilepsy severity proxy.

6.1.2 Objective #2

The second objective for this thesis was to explore the extent to which epilepsy worry correlates with anxiety and depression in AYAs with childhood-onset epilepsy. It is well recognized that anxiety and depression often co-occur, and these two conditions are prevalent in people with epilepsy. Worry is also often interpreted as the same construct as anxiety, and has been shown to be associated with both anxiety and depression in past studies (21,86,87), as well as in people with epilepsy (37,123). Examining the extent of correlation between the constructs of epilepsy worry, anxiety, and depression in people with epilepsy could help inform whether epilepsy worry is a separate construct that requires its own attention instead of being viewed as a part of anxiety or depression.

In our study, a strong positive correlation was found between anxiety and depression, which is consistent with our expectations, and provides additional evidence supporting the associations between these two conditions in epilepsy. Although highly correlated, anxiety and depression have been found to impact QoL differently in people with epilepsy (123,124). In terms of epilepsy worry, this thesis found that epilepsy worry had a weak positive correlation with anxiety and a moderate positive correlation with depression. Several other studies have examined the associations between epilepsy worry, measured using versions of QOLIE, and anxiety and depression in people with epilepsy. Two studies found that epilepsy worry was associated with anxiety but not with depression (124,125), and another study found that both anxiety and depression were associated with epilepsy worry, with anxiety having a stronger association (123). The differences in the strength of the correlation or associations may be due to differences in the instruments used to measure anxiety and depression in these studies, as instruments for the same constructs sometimes have variations and are not always interchangeable. The low or moderate correlations between epilepsy worry and anxiety/depression suggest that at least part of epilepsy worry is distinct from anxiety and from depression, although more evidence is needed to support this interpretation.

The weak correlation between epilepsy worry and anxiety found in the current study suggests a small overlap between these two constructs. Previous literature has attempted to differentiate between worry and anxiety by ascribing somatic responses to anxiety and cognitive processes to worry (22,24). It could be that the instrument used to measure anxiety in our study (STAI: Y-6) places more focus on the somatic responses, therefore resulting in a weak correlation with the cognitive processes of worrying about epilepsy.

6.1.3 Objective #3

The third and final objective for this thesis was to explore the extent to which parents of AYAs with childhood-onset epilepsy experience worry regarding their child's health, and whether it mediates the effect of epilepsy severity on AYAs' epilepsy worry. Due to the many adverse effects of epilepsy, parents of children with epilepsy may express heightened worry and concern about their child and adopt an over-protective parenting style, which in turn influences their child's psychosocial development and well-being (66,67,69). In this thesis, it was found that the level of parents' worry regarding their child's health eight years after epilepsy diagnosis was low overall. The parents' worry was not a risk factor for the AYAs' epilepsy worry, nor did it mediate the effect of the AYAs' epilepsy severity on AYAs' epilepsy worry. The mild levels of parental worry and the insignificant associations or mediating effects in the findings may again be due to the fact that the majority of AYAs in the sample have fairly mild epilepsy severity, which may not have strongly impacted the AYAs' functioning and family environment, thereby lessening the parents' caregiving stress and level of worry. This interpretation is supported by previous studies: One study found that parents of children with poorly controlled epilepsy had lower QOL, higher levels of anxiety, and higher levels of depression compared to parents of children with well-controlled epilepsy (58), and another study found that families of children experiencing more frequent seizures had higher levels of family stress compared to those who had less frequent seizures or had no chronic illness (126). The low variation in the AYAs' level of epilepsy worry and

epilepsy severity may have also contributed to the insignificant associations with and mediating effects of parents' worry.

6.2 Strengths

This thesis has several strengths. This is the first study to the best of our knowledge that focused on epilepsy worry among people with childhood-onset epilepsy a decade after their epilepsy diagnosis and examined the possible risk factors. The majority of the AYAs in our sample had been seizure-free for at least five years, which is consistent with the course of epilepsy (7). This thesis made use of the prospective nature of the data from HERQULES to allow temporality between exposure, mediator, and outcome variables. The exposures and mediator assessed in this thesis were all measured using validated instruments. Lastly, HERQULES contained multiple waves of follow-up which reduced the risk of recall bias.

6.3 Limitations

There are some limitations to this thesis. First, this thesis is a secondary analysis—HERQULES data were originally collected with the primary objective to assess HRQoL in children with epilepsy and the associated risk factors (83) other than epilepsy worry. As such, the study did not collect all potential risk factors of epilepsy worry (e.g., parents' anxiety, parenting style). Also, as most of the AYAs in the sample had mild epilepsy severity and none of the AYAs had surgical treatment, the generalizability of this study is limited to those with childhood-onset epilepsy and not those with more severe forms of epilepsy or drug-resistant epilepsy. There were some significant differences between the families retained in the study and the families lost to follow-up, with most of the differences indicating that the families lost to follow-up fared worse on child co-morbid problems, parents' psychological well-being, and family environment. The loss of variability among these factors lowered the likelihood of finding significant effects of these variables on the outcome. The sample size of this study may have also been underpowered to detect a significant effect, especially concerning the analysis regarding

the level of epilepsy worry among those who experienced epilepsy worry. Lastly, the tool used to measure epilepsy worry was not optimal. Requiring different age-appropriate versions of an instrument for specific age groups is a common challenge in long-term prospective studies. Two different versions of the QOLIE instrument, one for adolescents aged 11-17 and one for young adults aged 18 or older, were used in the questionnaires for the AYAs in HERQULES. Due to some differences in the questions included in the seizure worry sections for these two versions of QOLIE, only select items were used to generate a common score for epilepsy worry. The validity and reliability of the outcome measure, as well as comparability to other studies, may have been impacted by this process. In addition, worry related to seizures are not limited to future seizures or injuries as epilepsy worry was measured in this thesis, but can also include other areas such as social embarrassment and future outcomes. Unfortunately, there is an absence of a standard definition and description of specific elements that should be included in the assessment of epilepsy worry, and the effort to produce a standard definition could be complicated by the diverse etiology and clinical characteristics of epilepsy.

6.4 Recommendations for Future Research

Future research on worry related to epilepsy and seizures should prioritize the task of standardizing the term used to refer to this construct and the included elements. A comprehensive systematic review and additional structured interviews could aid in the development of a gold standard instrument for assessing epilepsy worry. Age group differences should be taken into consideration when developing the instrument, as people at different life stages place importance on different aspects of life. With the development of an instrument, future studies could consider examining epilepsy worry starting at epilepsy diagnosis to observe its trajectory and identify possible risk and protective factors. Future studies using a larger sample size could examine the association between the presence and level of epilepsy worry and various risk factors that this thesis was underpowered to assess or risk factors that were not included in this

thesis (e.g., type of AED). Future studies could also investigate the effect of providing reassurance to those in remission but on AEDs on reducing epilepsy worry. It would also be helpful to examine the potential positive effects of epilepsy worry—for example, an adequate level of worry toward epilepsy may help people avoid seizure triggers and adhere to their treatment regimens. Although the current study did not find an association between epilepsy severity and epilepsy worry, future studies could consider examining whether change in epilepsy severity can influence epilepsy worry. Lastly, continued research on improving treatment options for epilepsy are warranted to work toward the treatment goal of a seizure-free status without adverse effects.

6.5 Implications and Conclusions

In summary, this thesis found that the majority of AYAs reported at the 10-year follow-up that they had not experienced any epilepsy worry within the past four weeks, but more than one-third reported that they had experienced at least some epilepsy worry. Five-year seizure freedom status and currently taking AEDs were risk factors for the AYAs' epilepsy worry 10 years after their diagnosis of epilepsy in childhood. This thesis also found that epilepsy worry was weakly and moderately correlated with anxiety and depression, respectively. More detailed investigations are needed with additional information on the AEDs and their effects to understand the relationship between AED use and epilepsy worry. Although AYAs who did not gain control of their seizures have higher odds of experiencing epilepsy worry, healthcare professionals may consider examining AYAs in remission to identify those who still worry about their epilepsy and offer reassurance about their condition. The finding that epilepsy worry was not strongly correlated with anxiety or depression suggest that it could be examined and addressed as its own aspect of mental health in people with epilepsy, both in research and clinical practices, although more research is needed to support this argument. Identifying people who are worried about their epilepsy could also help identify those who are at risk for factors previously been found to be associated with epilepsy worry, such as attitude toward illness, internalized stigma, and self-efficacy in managing

seizures, with an aim toward targeting intervention efforts. Lastly, although parent and family factors were not found to affect AYAs' epilepsy worry, these factors still play an important role in the child's development and well-being, and should continue to be considered in future research regarding the mental health of people with childhood-onset epilepsy.

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Appendices

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 currently: _____

10. Number of AEDs total: _____

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

12. Does the patient have behavioural problems?

☐ No (normal)

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

Diagnosis: _____

13. Does the patient have cognitive problems?

☐ No (normal)

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

Diagnosis: _____

14. Does this patient have motor problems?

☐ No

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

Diagnosis: _____

15. Other neurological deficits? Please specify: _____

_____

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

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

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

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

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

Appendix B: AYA Questionnaire Measurement Tools

Spielberger State-Trait Anxiety Inventory short-form (STAI: Y-6)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
a) I feel calm	1	2	3	4
b) I am tense	1	2	3	4
c) I feel upset	1	2	3	4
d) I am relaxed	1	2	3	4
e) I feel content	1	2	3	4
f) I am worried	1	2	3	4

Centre 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 Questionnaire Measurement Tools

Family Inventory of Resources for Management (FIRM): Family Strength: Mastery and Health and Extended Family 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

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

Family Inventory of Life Events & Changes (FILE)

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

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

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

Did the change happen in your family:	During the last 12 months **Yes**	**No**	**Score**
I. Intrafamily Strains a. Increase of husband/father's time away from family			46
b. Increase of wife/mother's time away from family			51
c. A member appears to have emotional problems			58
d. A member appears to depend on alcohol or drugs			66
e. Increase in conflict between husband and wife			53
f. Increase in arguments between parent(s) and child(ren)			45
g. Increase in conflict among children in the family			48
h. Increased difficulty in managing teenage child(ren)			55
i. Increased difficulty in managing school age child(ren) (6-12 yrs)			39
j. Increased difficulty in managing preschool age child(ren) (2.5-6 yrs)			36
k. Increased difficulty in managing toddler(s) (1-2.5 yrs)			36
l. Increased difficulty in managing infant(s) (0-1 yr)			35
m. Increase in the amount of "outside activities" which the children are involved in			25
n. Increased disagreement about a member's friends or activities			35
o. Increase in the number of problems or issues which don't get resolved			45
p. Increase in the number of tasks or chores which don't get done			35
q. Increased conflict with in-laws or relatives			40
II. Marital Strains a. Spouse/parent was separated or divorced			79
b. Spouse/parent had an "affair"			68
c. Increased difficulty in resolving issues with a "former" or separated spouse			47
d. Increased difficulty with sexual relationship between husband and wife			58

Did the change happen in your family:	During the last 12 months Yes	No	Score
III. Pregnancy and Childbearing Strains			
a. Spouse had unwanted or difficulty pregnancy			45
b. An unmarried member became pregnant			65
c. A member had an abortion			50
d. A member gave birth to or adopted a child			50
IV. Finance and Business Strains			
a. Took out a loan or refinanced a loan to cover increased expenses			29
b. Went on welfare			55
c. Change in conditions (economic, political, weather) which hurts the family investments			41
d. Change in agriculture market, stock market, or land values which hurts family investments and/or income			43
e. A member started a new business			50
f. Purchased or built a home			41
g. A member purchased a car or other major item			19
h. Increased financial debts due to over-use of credit cards			31
i. Increased strain on family "money" for medical/dental expenses			23
j. Increased strain on family "money" for food, clothing, energy, home care			21
k. Increased strain on family "money" for child(ren)'s education			22
l. Delay in receiving child support or alimony payments			41
V. Work-Family Transitions and Strains			
a. A member changed to a new job/career			40
b. A member lost or quit a job			55
c. A member retired from work			48
d. A member started or returned to work			41
e. A member stopped working for extended period (e.g., laid off, leave of absence, strike)			51
f. Decrease in satisfaction with job/career			45
g. A member had increased difficulty with people at work			32
h. A member was promoted at work or given more responsibilities			40
i. Family moved to a new home/apartment			43
j. A child/adolescent member changed to a new school			24
VI. Illness and Family "Care" Strains			
a. Parent/spouse became seriously ill or injured			44
b. Child became seriously ill or injured			35
c. Close relative or friend of the family became seriously ill			44
d. A member became physically disabled or chronically ill			73

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

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

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

Appendix D: Comparison of Characteristics of Complete and Incomplete Cases

Table D-1: Comparison of AYA characteristics of complete and incomplete cases.

Characteristics	Incomplete data (n = 39)	Complete data (n = 91)	p-value
AYA sex, n (%)			
Male	15 (38.46)	47 (51.65)	0.17
Female	24 (61.54)	44 (48.35)	
AYA age, mean (SD)	17.87 (2.60)	17.80 (2.56)	0.89
Epilepsy worry experienced, n (%)			
Yes	16 (41.03)	34 (37.36)	0.69
No	23 (58.97)	57 (62.64)	
Epilepsy worry level, mean (SD)	0.99 (1.05)	1.00 (0.97)	0.98
AYA depression, mean (SD)	14.31 (12.18)	12.58 (10.39)	0.41
AYA anxiety, mean (SD)	38.24 (14.06)	36.56 (13.41)	0.53
5-year seizure freedom, n (%)			
Yes	24 (64.86)	58 (63.74)	0.90
No	13 (35.14)	33 (36.26)	
Current use of AEDs, n (%)			
Yes	11 (30.56)	23 (25.27)	0.55
No	25 (69.44)	68 (74.73)	
Epilepsy severity, mean (SD)	6.33 (1.00)	6.31 (1.13)	0.92
Seizure type, n (%)			
Generalized	13 (61.90)	32 (35.16)	0.09
Partial	8 (38.10)	55 (60.44)	
Undetermined	0 (0)	4 (4.40)	
Behaviour comorbidities, n (%)			
Yes	6 (21.43)	11 (12.09)	0.22
No	22 (78.57)	80 (87.91)	
Cognitive comorbidities, n (%)			
Yes	2 (7.41)	22 (24.18)	0.06
No	25 (92.59)	69 (75.82)	

AYA, adolescent and young adult; AED, anti-epileptic drug.

Table D-2: Comparison of parent and family characteristics of complete and incomplete cases.

Characteristics	**Incomplete data** (n = 39)	**Complete data** (n = 91)	**p-value**
Parental age, mean (SD)	49.00 (6.34)	48.77 (4.84)	0.84
Parental depressive symptoms, mean (SD)	9.17 (8.49)	10.36 (9.07)	0.53
Parental worry, mean (SD)	76.23 (24.63)	67.03 (26.58)	0.08
Parental marital status, n (%)			
Currently married	23 (79.31)	76 (83.52)	0.60
Not currently married	6 (20.69)	15 (16.48)	
Family income, n (%)			
Less than $50,000	4 (15.38)	15 (16.48)	
$50,000 - $99,999	9 (34.62)	29 (31.87)	0.29
$100,000 - $149,000	3 (11.54)	25 (27.47)	
$150,000 or more	10 (38.46)	22 (24.18)	
Family resources, mean (SD)	51.45 (10.36)	51.71 (12.39)	0.92
Family demands, mean (SD)	8.45 (5.19)	8.43 (6.11)	0.99
Family adaptation, mean (SD)	13.97 (3.22)	14.78 (4.19)	0.34

Curriculum Vitae

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Presentations:

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