Impact of waiting time for first clinic assessment and seizure outcomes of pediatric epilepsy

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ABSTRACT

Introduction: Pediatric epilepsy has increased in global incidence. Children with epilepsy require immediate healthcare evaluation and monitoring. Waiting times between first seizure onset and pediatric neurology assessment may impact seizure outcome at follow-up. Quality of medical care for children with first seizure onset will be assessed and the impact of pediatric neurology clinic waiting times on seizure outcomes will be determined.

Methods: This retrospective study, based on chart review, includes patients with first seizure evaluation at the Royal University Hospital in Saskatoon between January 2012 and December 2015. The interim period before first assessment and other factors were studied in relation to seizure outcome on follow-up.

Results: 1158 patients were assessed. 197 patients had epileptic events. The mean age of patient at diagnosis was 6.2 years (±5.2). The mean waiting time for assessment by a pediatric neurologist was 4.3 (±3.6) months. The mean duration of follow-up was 20.9 (±11.0) months. At the last seizure assessment, 132 patients were seizure-free and 65 patients had seizure recurrence. Factors independently associated with poor seizure outcome included waiting time, language not age-appropriate, and gait not age-appropriate. Factors collectively associated with poor seizure outcome included waiting time and gait not age-appropriate. Total number of anti-epileptic drugs was significant at 18 months in both univariate and multivariate models.

Conclusion: First seizure assessment is crucial for management of children with epilepsy. Waiting time and other factors may influence seizure outcome, representing opportunities to improve standard medical care.

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DEDICATION

This thesis is dedicated to my grandmother, Taj Begum, a beautifully kind, loving, and caring soul.

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LIST OF ABBREVIATIONS

AED - Anti-Epileptic Drug

CHS - Community Health Survey

CI - Confidence Interval

CT - Computerized Tomography

EEG - Electroencephalogram

ILAE - International League Against Epilepsy

IQ - Intelligence Quotient

MRI - Magnetic Resonance Imaging

NLSCY - National Longitudinal Survey of Children and Youth

NPHS - National Population Health Survey

OR - Odds Ratio

RUH - Royal University Hospital

SD – Standard deviation

SEEG - Stereoelectroencephalography

SES - Socioeconomic Status

SHR - Saskatoon Health Region

SK - Saskatchewan

CHAPTER 1: INTRODUCTION

1.1 Overview

Epilepsy is a severe condition that encompasses a multitude of serious symptoms and requires unique medical treatment from a specialist. This disease is most common amongst children and therefore requires the attention of a pediatric neurologist (Engel et al., 2005). In order to receive service, there is a period of waiting time between the first seizure experienced and the first visit to a pediatric seizure clinic for diagnosis and treatment. This period of waiting time can have an immense impact on the development of a child and further necessitates the urgency for treatment (Appleton et al., 1998; Berg et al., 2014; Clare et al., 1978). This study will explore the impact of not receiving urgent medical attention for a first suspected seizure and determine how this affects the seizure outcome of children with an onset of epilepsy, whether that involves transitioning to a seizure-free state or continuing to have further seizure treatment provided by a physician.

1.2 Rationale

Epilepsy is one of the most common serious neurological disorder in existence (WHO, 2019). This is a problem in Saskatchewan where there is only one pediatric seizure clinic. Saskatoon

and its surrounding area is within a centralized location, however, the rest of the province often has to rely on their own resources for further medical assistance before being seen by a specialist in Saskatoon. This presents an issue when travelling from rural and remote areas of the province where transportation services are not as convenient or readily attainable.

Accurately understanding the impact of waiting times on child development is crucial because of the critical period of growth that childhood calls for. A clear understanding of the factors associated with waiting time in a pediatric epilepsy clinic could help in deciding which interventions will have the greatest impact in improving the clinical course of epilepsy and resiliency.

The results of this study can prospectively improve the quality of patient care by indicating the developmental impact of a child who experiences a seizure and requires medical attention. This notion is not currently well understood enough to benefit from and it could make a difference towards how pediatric neurologists prioritize their visits and time, reducing waiting times for first seizure clinical evaluations.

By understanding and informing the Saskatoon Health Region (SHR) of its waiting times in pediatric epilepsy services, Saskatchewan populations outside of the SHR should have better access to these services. This study will also advise the Health Sector of the Government of Saskatchewan and the SHR under investigation on best practices and provide evidence for sustaining optimal epilepsy and pediatric epilepsy health services in the province. This will improve the flow of pediatric health services which will in turn benefit patients, families, and hospital staff.

1.3 Purpose of the study

The purpose of the study is twofold:

1.3.1 Primary purpose

A first seizure clinic appointment is crucial for a child because of the critical period of brain maturation and growth involved; therefore, the main purpose of this study is to understand the effects of pediatric seizure clinic waiting times between a first suspected seizure and a first clinic appointment. This will be achieved by recognizing epileptic children with the highest risk of a poor seizure outcome based on a number of independent seizure variables including: sex, age, residential location, seizure type, frequency, and treatment.

1.3.2 Secondary purpose

The results of this study will lead to improving the quality of patient care by identifying seizure management and the developmental impact of a child with a diagnostic delay. This notion is not currently understood to its full benefit and it has the potential to change how physicians prioritize their time, shortening the waiting time of first clinical evaluations. Additionally, health service authorities may need to extend the medical care resources and this study would identify that.

1.4 Research objectives

There are four objectives in this study:

Objective 1. To identify whether the waiting time experienced between seizure onset and

first clinic appointment for diagnosis by a pediatric neurologist has an impact on a child's seizure outcome;

Objective 2. To identify whether language development is associated to seizure outcome;

Objective 3. To identify whether motor development is associated to seizure outcome; and

Objective 4. To identify whether residential location are associated to seizure outcome

CHAPTER 2: LITERATURE REVIEW

2.1 Overview

This section includes a brief introduction of pediatric epilepsy. The epidemiology of pediatric epilepsy at a global, national and local level is also discussed. Measures of the illness and precipitating factors will also be depicted.

2.2 Background of pediatric epilepsy

Epilepsy is a unique and complex condition involving a large variety of symptoms and presentations. This can be problematic for parents, guardians, and close social networks as well as professionals working in the health sector since the care of each epileptic child varies. Epileptic children are disadvantaged by various developing skills such as language, motor, and cognitive functions when compared to the general childhood population (Desai, 2008). Cognitive impairments observed in epileptic children include deficits in attention, memory, academic success, and lower mean IQ scores (MacAllister & Schaffer, 2007). These children also demonstrate problems with social development and stigma because of these impairments (Austin et al., 2004).

Pediatric epilepsy is a neurological condition involving the rapid and unexpected altercation in how brain cells transmit electrical signals causing children to have seizures (Al-Biltagi, 2014).

Epilepsy can be a chronic condition or it can involve recurring seizures. A seizure presents itself when there is an abrupt discharge or disturbance of the electrochemical firing of neurons that cause altercation to an individual's sensation, perception, or behaviour (DuLac, MacDonald, & Kelly, 1995). Numerous factors contribute to the medical and psychosocial difficulties faced by epileptic children. Investigating potential methods of minimizing this impact, such as maximizing the child's involvement in normal childhood activities, can benefit the wellbeing of children and in turn, their families (England et al., 2012). Currently, there are gaps in the research regarding the relationship between various seizure-related variables and developmental impact. With awareness to this gap, the next step for researchers is to determine the impact of seizure-related variables on the impact of children who are diagnosed with epilepsy.

2.3 Epidemiology of pediatric epilepsy

2.3.1 Global

Over 50 million individuals worldwide have active epilepsy (WHO, 2019). About 20% (10.5 million) are children under 15 years old (Guerrini, 2006). There are 3.5 million individuals diagnosed with epilepsy each year and 40% of them are under 15 years old. More strikingly, only 20% of these children live in developed countries (Guerrini, 2006). Population-based studies on pediatric epilepsy indicate annual incidence rates of 61-124 per 100,000 in developing countries while the annual incidence is 41-50 per 100,000 in developed countries (Guerrini, 2006). Incidence gradually decreases from an estimate of 150 per 100,000 in the first year of life to 45-50 per 100,000 after a child reaches the age of 9 years old (Guerrini, 2006). Cumulative incidence studies provide evidence that up to the age of 15 years old, 1.0-1.7% of children will have a minimum of one unprovoked seizure, and 0.7-0.8% will experience repeated seizures (Guerrini, 2006). Frequency rates in North America and Europe vary between 3.6-6.5 per 1000 in contrast to African and Latin American studies that report rates of 6.6-17 per 1000 (Guerrini, 2006).

In the USA, a substantial proportion of those with uncontrolled (refractory) epilepsy are uninsured, have a lower socioeconomic status (SES), and reside in rural dwellings (Kenney & Mann, 2013). About 20% of the country's citizens live rurally but only 9% of its physicians practice in these areas. It is the characteristics of this vulnerable population such as this that deter the ability to self-manage ongoing care needs and comply with prescribed therapies, leading to greater usage of critical health care resources, such as emergency departments (Kenney & Mann, 2013).

About 80% of those with epilepsy are living in low- and middle-income countries and 75% of them may not receive appropriate treatment (WHO, 2019). This includes children in Nigeria, China, Pakistan, and Panama (WHO, 2010).

2.3.2 Canada

Epilepsy Canada considers epilepsy to be a neurological disorder affecting an average of 15,500 individuals every year (Epilepsy Canada, 2016) and the incidence of pediatric epilepsy in Canada is 41 per 100,000 children per year (Camfield, 1996). Of this number, 44% are diagnosed before the age of 5, 55% are diagnosed before the age of 10, and 75-85% of those with epilepsy are diagnosed before age 18. Prior to turning 14 years old, 1% of diagnosed children have recurrent seizures (Epilepsy Canada, 2016). In approximately half of epileptic children, seizures disappear completely, a statistic which illustrates the vast number of children who bring symptoms into adulthood.

Estimates of the prevalence of pediatric epilepsy largely depend on how epilepsy is defined. Two cycles of data were analyzed based on cycles conducted from the National Longitudinal Survey of Children and Youth (NLSCY) between 1996-1997 and 1998-1999 (Prasad, 2011). Families were asked if their child had epilepsy that had been diagnosed by a health care professional. The prevalence for children between 0-13 years was 4.03 per 1, 000 and it was 5.26 in the age groups 0-15 years old (Prasad, 2011).

Age-specific incidences of pediatric epilepsy were 118 for every 100,000 children younger than 1 year, 48 per 100,000 from 1 to 5 years, 43 per 100,000 from 6 to 10 years, and 21 per 100,000 from 11 to 15 years (Camfield et al., 1996).

The incidence and prevalence rates of pediatric epilepsy illustrate that the illness is a considerably common condition that not only can impact numerous children and households across Canada but can also occur multiple times in the same child.

A Canadian study conducted in Manitoba (Kozyrskyi & Prasad, 2004) observed the province's rural south, the north, Winnipeg, and Brandon. The study focused on the impact of access in residing in a rural environment versus an urban environment towards pediatric health care services and if socioeconomic status (SES) has an impact on access.

Age-specific prevalence rates for pediatric epilepsy in Manitoba were determined by health care administrative records. Higher prevalence rates were discovered in children of all ages living in lower SES neighbourhoods in urban areas, which showed a gradient of higher prevalence amongst lower levels of income (Kozyrskyi & Prasad, 2004).

Population-based health care administrative data was used to describe the geographical distribution of pediatric epilepsy. The data collected in the study by Kozyrskyi and Prasad (2004) suggested that the burden of seizure disorders is not evenly distributed among children. The association with income was strongest in the youngest and oldest children. In rural areas, children 5 years and younger and with lower levels of SES had a greater prevalence of seizure disorders (Kozyrskyi & Prasad, 2004).

2.3.3 Saskatchewan

There are only self-reported prevalence rates of epilepsy in Saskatchewan. The Community Health Survey (CHS) indicates the prevalence is 5.0 per 1000 whereas the National Population Health Survey (NPHS) indicates a prevalence of 5.2 per 1000. These are not age-specific rates

but CHS only surveys individuals 12 years and older whereas the NPHS includes individuals from all age groups (Tellez-Zenteno, 2004).

2.4 Waiting time outcome in pediatric epilepsy

First clinic visits are an important consideration in confirming seizure diagnosis, addressing appropriate management of the illness, and counseling parents about their stressful concerns regarding the newly diagnosed illness (England et al., 2012). Waiting for the first appointment can be a strenuous experience for the parent and the child who may have a potential of epilepsy.

Jallon et al (2001) observed first unprovoked seizures and those with previously undiagnosed epilepsies at initial presentation in a large cohort of 1942 patients comprised of both children and adults. In this study, the time between first seizure and epilepsy diagnosis ranged from 1 day to 52 years, with an average of 7 months. Seizures were undiagnosed due to a lack of access to medical care, unawareness of the illness, and patients believed they previously had medical attention but the events were not diagnosed as seizures.

Berg et al (2014), a researcher in the effects of waiting times on pediatric epilepsy, observed how diagnostic delays (hereinafter termed as waiting times) impact the development of children and factors that affect waiting times. Their study supported the hypothesis that waiting times correspond to less ideal developmental outcomes. Results were considerably poorer in those delayed over a month. A number of variables were incorporated: seizure type, presentation, parental education, and the epileptic child's ability to tolerate drugs. The effect of waiting times was significant with greater waiting times leading to poorer scores in a number of areas: verbal comprehension, perceptual organization, processing speed, and freedom from distractibility. Relative percentages also indicated that 41% had lengthened waiting times. Reasons for those who experienced lengthened waiting times were attributed to having parents who did not recognize the events as seizures, having pediatricians or neurologists miss or defer

the diagnosis, and experiencing scheduling problems. Waiting times, for those who experienced delay, included 21% who were diagnosed between one month and four months; 7% who were diagnosed between four months and a year; and 13% who were diagnosed over a year later (Berg et al., 2014).

Berg et al (2014) documented waiting time outcomes for seizures as associated with the developmental impact of children. A primary weakness in their research is that it takes place in a comparatively affluent U.S state (Connecticut) with two large hospitals, seventeen practicing specialists, and a state population size of roughly half a million children. Consequently, this study was conducted in an environment with better than average access to specialists and the results may represent what occurs in optimal situations but not in a majority of other geographical environments. The province of Saskatchewan is in a much less ideal state since there is only one hospital with a seizure clinic. Further, there are currently only three full-time pediatric neurologists and one part-time pediatric neurologist that work at the province's seizure clinic.

Since the implementation of Berg's study over twenty years ago, there has been no significant change in the clinical pathway in North America (Berg et al., 2014). There is a lack of change in the health care system. In order to rise above hurdles regarding access and navigation, an unrelenting effort to build and reinforce partnerships between the stakeholders who deliver pediatric health care is essential. Through persistent efforts to improve integration, access can be improved as the coordination between the hospital setting and the community setting can be strengthened.

An ideal situation for the Saskatchewan pediatric epilepsy clinic would be to mimic a system of the development of care pathways such as the system currently implemented in the United Kingdom. The United Kingdom's system urges pediatric neurologists to meet with every child patient who presents with a first onset of suspected seizures to be seen within two weeks and up to a month of that event as a way to reduce lapsed time between an appointment and the event (Berg et al., 2014). This is challenging for a health region with only one seizure clinic and

only four pediatric neurologists but it would be largely beneficial in reducing the issues that are involved in having a delayed diagnosis such as a poorer seizure outcome and those affecting the course of child development.

The length of time that it takes to wait for a diagnosis from a pediatric neurologist after a seizure event can be a critical period for children and families. In our study, this time lapse is termed as waiting times and can alter a child's ability to recover after experiencing their first seizure.

2.5 Seizure outcomes

Seizure outcome is of interest in our study as it has been shown to lead to better results when waiting times for clinical diagnosis and treatment of pediatric epilepsy are minimized. This section will provide an understanding of seizure outcome, how it has been defined in the literature, and how it will be defined in our study.

A retrospective study on seizure outcomes in pediatric epilepsy by Dragoumi et al (2013) stratified seizure outcomes by dividing the clinical courses of participants into a spectrum of four categories describing subjects' exclusive patterns of clinical course. This classification followed the methodology used in an earlier study involving children and adults with newly diagnosed epilepsy by Brodie et al (2012). Pattern A: an "excellent" clinical course where children became seizure-free early on and remained so during follow-up investigations; Pattern B: a delay in seizure freedom for over a year after starting treatment but subjects remained seizure-free during follow-up investigations and thus were classified as "improving"; Pattern C: a "relapsing" clinical course with periods of seizure freedom lasting more than a year interspersed with relapses; and Pattern D: a "poor" clinical course, involved subjects that were drug-resistant throughout follow-up investigations, meaning the medicine prescribed was not successful in improving the status of their seizure outcome. Under this categorization, predictors of an excellent clinical course were those with an early response to antiepileptic drug

(AED) therapy and being between ages 6 to 9 years old at the onset of epilepsy. Clinical variables identified with a poorer prognosis included association with multiple seizure types, young age at seizure onset (within the first year of life), and having an associated history of migraines.

It is evident that studies have defined seizure outcome in various ways. For the purpose of our study, seizure outcome will have two possibilities: seizure-freedom (no longer experiencing seizures) or experiencing persistent seizures.

2.6 Potential factors influencing waiting time and seizure

Many studies have been published on the factors effecting waiting times in pediatric epilepsy. The literature review focuses on environment, population characteristics and health management. Information on most of these covariates were available for observation in this study. This section of the literature review provides an overview of the variables affecting waiting time and seizure.

2.6.1 Patient-Related Characteristics

Patient-related characteristics include both social demographic factors (factors that make the patient susceptible to pediatric epilepsy) and clinical characteristics (factors that influence utilization of the pediatric seizure clinic services), both of which characterize the patients included in this research.

2.6.1.1 Social demographic factors

Research in pediatric epilepsy commonly assesses the effects of social demographic factors. These variables are repeatedly studied due to the disparities seen in the number of pediatric epilepsy cases seen across various demographics: residence, age, and sex. Each of the variables

listed were factors included in our collection of data. A review of these social demographic factors is written below.

2.6.1.1.1 Sex

Sex-specific incidence rates are consistently higher in males than females. Sex differences in the incidence of risk factors for epilepsy could be due to a higher incidence of increased central nervous system infection in males (Kotsopoulos et al., 2002).

2.6.1.1.2 Age at seizure onset

Seizures can present themselves throughout an individual life course at any given age. Those in their first year of life are at the highest risk of experiencing seizures (Dragoumi et al., 2013). The literature generally illustrates that an early age of onset coupled with a long duration of epilepsy have a dismal influence on the patients' language and cognitive abilities (Dragoumi et al., 2013).

Age-specific incidence rates show that epilepsy peaks when children are under one year old (Epilepsy Canada, 2016). As individuals age, incidence rates gradually decrease and remain low until individuals are over 60 years old (Epilepsy Canada, 2016). Older age is documented as a protective factor significantly associated with shorter durations of epilepsy (Aguglia, 2011; Teutonico et al., 2013). Conversely, studies that included patients of all ages did not demonstrate a consistent effect of age at onset on prognosis (Annegers, 1979; Berg, 2001; MacDonald, 2000). This is an important demographic factor to consider and as such, in our study, we have taken into account the age the children were when they experienced their first seizure.

2.6.1.1.3 Age at diagnosis

Children often have recurring seizures or symptoms once they develop an onset of seizures. As stated previously, this is a risk of recurrence up until the age of 14 years old (Epilepsy Canada, 2016). In our study, we have taken into account the age of the child subject at the time diagnosis.

2.6.1.1.4 Residence

Residence, as noted previously, shows much higher incidences and prevalences of pediatric epilepsy in developing countries than in developed countries (Guerrini, 2006). The disparities of rural and urban locations are also prevalent when it prevents individuals seeking care from obtaining the necessary treatment.

There is a shortage of pediatric neurologists in Saskatchewan and although the population of the province has vastly grown in the past twenty years, there has not been much of a proportional increase in much of its medical and health care staff. Since our study takes place at the only seizure clinic in Saskatchewan, the Royal University Hospital (RUH), we compare epileptic children from rural and urban communities within the province in order to gage the effects of this factor in the province.

According to the Canadian Health Commission, geography is a health determinant (Romanow, 2002). 'Rural' and 'urban' locations are terms that are commonly used to decipher the allocation of resources across provinces. Canada is in a better position than the rest of North America because insurance is less of an issue but the characteristics of those in rural versus urban dwellings still exist and the shortage of physicians practicing in rural communities is still apparent. However, there are specific studies in Canada and abroad that did not find differences in the prevalence of epilepsy but did find higher prevalence rates when looking at socioeconomic status, even within urban neighbourhoods (Kozyrskyj et al., 2004; Abib et al., 2007).In our study, we have used rural locations to indicate those residencies located outside of

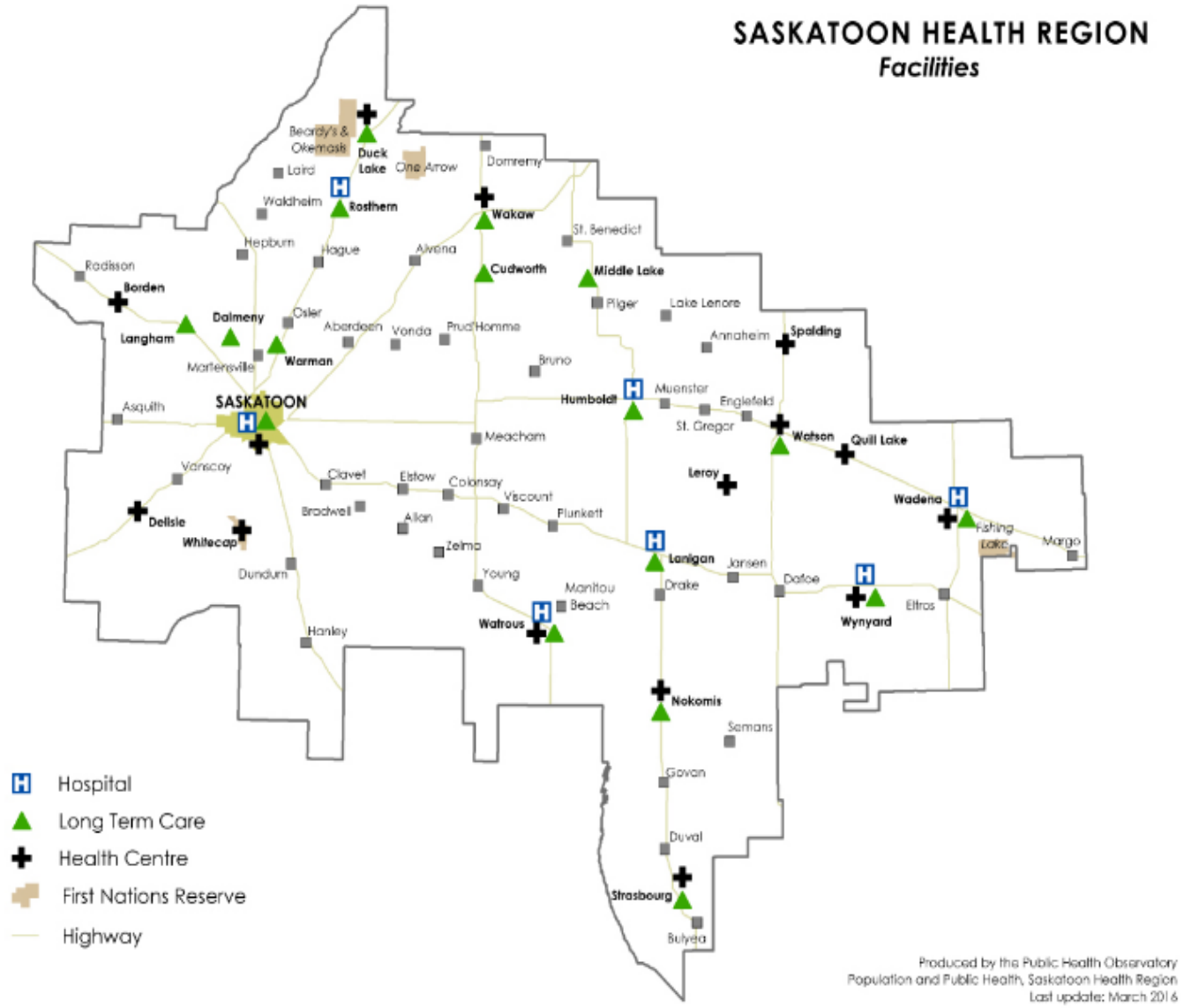
the Saskatoon Health Region (SHR) and urban location to indicate those residencies located within the SHR.

Although Saskatchewan is a relatively expansive province, it encompasses only one seizure clinic which is located in the city of Saskatoon. It may be a challenge for some families that reside in rural or remote areas of the province to find a means of transportation and subsequently find treatment and in some cases, families have to resort to visiting a pediatric neurologist in other provinces, particularly those sharing a boundary such as Alberta or Manitoba.

Urban and rural disparities are a reality for many parts of the world including the province of Saskatchewan. Rural versus urban health care access is a social dimension that is encountered in a wide variety of geographical settings around the globe. Great disparities in access to medical services exist between urban and rural populations where urbanized dwellers seem to have better access to resources while rural dwellers are deficient in a number of social opportunities.

The Saskatoon Health Region (SHR) represents roughly 5 % of Saskatchewan's geographical boundaries, yet 35 % of those who receive hospital services in the city of Saskatoon live outside of the SHR's geographic land base (Saskatchewan Ministry of Health, 2008). For further reference, a map of SHR is displayed in Figure 2.1. One might consider the disparities in health care services between those residing in cities within SHR and those outside of SHR can be attributed to Saskatoon being the most populous city in the province, yet the population of Saskatoon comprises of no more than 20 % of the province (Government of Saskatchewan, 2011).

Figure 2.1: Map of Saskatoon Health Region (SHR)



Neudorf et al. (2009)

2.6.1.2 Clinical factors

Research in pediatric epilepsy typically observes the effects of clinical or seizure-related variables for an understanding of their impact. These variables are repeatedly studied due to the disparities seen in the number of clinical features of epileptic children: seizure type, age at seizure onset, seizure frequency, gait, and language. A review of these clinical factors is provided below.

2.6.1.2.1 Seizure type

There is a challenge involved in defining seizures in a clinical sense because epilepsy is an umbrella term that encompasses numerous forms of seizures and symptoms as well as presentations. The International League Against Epilepsy (ILAE) has created the classification system that is the most commonly used way of defining epilepsy and seizure disorders (ILAE, 1989). Under the ILAE classification system, two main seizures types are distinguishable: partial seizures and generalized seizures.

Univariate and multivariate analyses have associated seizure type with seizure outcome (Arts, 1999; Huang et al., 2014; Jayalakshmi et al., 2011; Teutonico et al., 2013). Partial seizures usually arise from a limited region of the brain. Partial seizures originate locally in the cortex and are typically preceded by a hallucination (of the visual, auditory, or olfactory nature) (Kaplan, 2003). This largely depends on the function of the area of the cortex where the seizure takes place.

As opposed to partial seizure activity which occurs laterally in the brain, generalized seizure activity occurs bilaterally (in both the left and right hemispheres of the brain) with consciousness abruptly lost; therefore, the patient does not experience a hallucination (Chadwick, 1994). Generalized seizures can be either brief experiences or events of longer duration. In our study, seizures are classified as partial or generalized as recommended by the ILAE.

2.6.1.2.2 Seizure frequency

Seizure frequency is often the term used to assess the activity and severity of epilepsy and the efficacy of treatment in obtaining seizure control. This is quantified in different ways in various studies of epilepsy (Aldenkamp, 1997). Seizure frequency is an important factor to consider in this study because an increased frequency of seizures has proven to interfere with brain development (Aldenkamp, 1997).

Seizure frequency is something typically assessed by all pediatric neurologists and this indicator was taken into consideration here. For the purpose of our study, seizure frequency categories were divided into those who experienced fewer than 10 seizures total and those who experienced more than 10 seizures total to decipher between those with a greater frequency and less frequent seizures. The rationale for this is that most children with epilepsy have 10 or fewer seizures, thus the division between a low and high frequency (Pellock et al., 2016).

2.6.1.2.3 Etiology

Etiology is the term used in pediatric epilepsy to describe the cause of the condition. The International League of Against Epilepsy (ILAE) described three categories: 1) unidentified/unknown; 2) genetic; and 3) structural/metabolic (Berg et al., 2001) and these are also the categories used in our study. An unidentified or unknown etiology means that the pediatric neurologist did not identify the etiology in physician notes and the cause is not known. A genetic etiology signifies that the origin of the condition comes from a genetic defect. Etiologies that are structural or metabolic originate from another structural or metabolic condition in which there is an acquired structural abnormality (usually during/prior to birth) or genetic where there is a separate condition between the genetic defect and the epilepsy condition. In our study, the etiologies of pediatric epilepsy were categorized following the three widely-used ILAE descriptions: 1) unidentified/unknown, 2) genetic, and 3) structural/metabolic.

2.6.1.3 Development

Development is a significant component of functionality and as such, it was a factor observed in our study. In particular, gait and language abilities were the components of development assessed.

2.6.1.3.1 Gait

Gross motor development is essential for daily living. It typically involves larger muscle movements of the limbs. Any sport or activity that involves greater movement falls under this category.

Research on motor involvement in children with epilepsy, aged between 7 and 17 years old, has shown significant deficits in gross motor and balance capabilities (Kowulski & Di Fabio, 1995). Significantly, 19 of the 21 children involved in the study by Kowulski and Di Fabio (1995) with an average age of 12.33 years performed below their age-level. These children were assessed on their single-leg stance, heel-to-toe walking, and gait. However, an earlier study conducted by Beckung and Uvebrant (1993) on a different sample of children who were epileptic but did not have mental retardation or cerebral palsy found only 9 of the 21 epileptic children included in the study experienced gross motor impairment. However, static and dynamic balances were not assessed in the study by Beckung and Uvebrant (1993). Further, Clement and Wallace (1990) found competitive sports were less popular with children who had epilepsy. Engaging in sports requires a great deal of balance and a strong gait, which supports a low desirability to engage in sport activity.

The incidence of new developmental problems of epilepsy in childhood and the variables that predict abnormal outcome or deterioration of developmental status have previously prospectively been studied at the Royal University Hospital in Saskatoon (Barnard & Wirrell, 1999). Researchers found that of the 17 children who were developmentally normal before

being diagnosed with epilepsy. Significantly, only 11 child patients had a normal presentation at follow-up.

Motor development is a fundamental aspect of human behaviour that is typically required to carry out daily functions. Gait is one basic area of gross motor development that pediatric neurologists assessed at the Royal University Hospital (RUH), thus, it is the motor development variable that has been collected in our retrospective study in order to assess development.

2.6.1.3.2 Language

Whether or not a child has appropriate expressive language for their age is one area of language that is assessed in seizure clinics. Language development is related to general cognitive development and language disorder can be commonly observed in those with pediatric epilepsy (Allen et al., 2016; Byars et al., 2013; Karrash et al., 2017; Selassie, 2008; Vanasse, 2005; Weiss et al., 2016; Zhao et al., 2014). Expressive language accounts for how humans are able to communicate and it is particularly important for children to let parents and caregivers understand their needs and emotions.

Byars et al. (2013), one of those who studied the effects of language in pediatric epilepsy, found that children with persistent seizures obtain poorer language scores, even at the onset of their seizures when compared to their siblings who do not experience recurrent seizures and peers with recurrent but not persistent seizures. Children with epilepsy also continue to show poorer language function three years after the onset of seizures even though their healthy siblings and children with recurrent seizures demonstrate progression in language skill (Byars et al., 2013).

Further, researchers have found that children with epilepsy experience other speech impairments that cause them to not communicate at a level appropriate for their age. Studies demonstrate that children with epilepsy experience pronunciation difficulty (Allen et al., 2016; Selassie, 2008; Vanasse, 2005). Such difficulty in pronunciation may also be problematic when

it comes to the demonstration of clear speech. These individuals are often difficult to understand because their oral sounds are not clear or precise.

Zhao et al (2014) found language development can be altered and degenerated in children with all types of pediatric epilepsy but those who experience partial seizures from the left hemisphere and temporal lobe, which is the area of the brain that controls the comprehension of words and speech, have much more difficulty with language than those who have other types of epilepsy.

For the purpose of our study and since there is restricted information that is available given the retrospective nature of it, whether or not the child was at the appropriate level of language development was the component assessed. This assessment was determined by the pediatric neurologist.

2.6.2 Health management

In this study, health management involves the way the pediatric seizure clinic services are used amongst patients with potential epilepsy. Treatment is the health management that was assessed in our study.

2.6.2.1 Treatment

There are a number of treatment possibilities available after a diagnosis of pediatric epilepsy has been ascertained and that treatment is necessary for the patient, including pharmacotherapy, ketogenic diet, vagus nerve stimulation, and surgery (Benbadis & Tatum, 2001). The three types of treatments that were collected in our study were antiepileptic drugs (AEDs), ketogenic diets, and surgeries. As a result, these are the three types of treatments that will be discussed in this literature review.

2.6.2.1.1 Anti-epileptic drugs (AEDs)

AEDs, or anticonvulsants, are a group of medications that help to control the frequency and severity of seizures (Kaiser, 2002; Lamberink, 2017). AEDs are the most widely-used form of treatment for pediatric epilepsy. However, this treatment type is not without its problems which include its effectiveness, compliance in the use of drugs as prescribed, and the side-effects that can result through intake. Previous studies show that response to the first drug is directly associated with seizure outcome (Dlugos et al., 2001; Kwan & Brodie, 2010; Schiller & Najjar, 2008; Sillanpää, 1993).

The goal of treatment in using AEDs is to reduce seizure frequency and enhance a patient's well-being with as few side effects, complementary medications, and long-term detrimental effects as possible. Most neurologists recommend waiting until after a child has had a second seizure before starting that child on AED therapy as confirmation that drug intervention is necessary (Miller & Drislane, 2007). There are, however, times when the risk of recurrent seizures is higher (such as with a tumor or infection) and immediate AED treatment may be warranted. However, a second seizure confirms that the risk of recurrence is greater and treatment with AEDs is typically necessary and signaled by such an event (Miller & Drislane, 2007).

Prospective studies that observed epileptic children from the onset describe most patients as seizure-free within the first few years of epilepsy (Oostrom et al., 2005; Shinnar & Pellock, 2002). AEDs tend to provide effective treatment for most children and can drastically help with seizure control. Nearly two-thirds of patients are able to end consumption of medication after they become seizure-free. However, 20%-30% of epileptic children are unaffected by AEDs and continue to experience seizures (Mikati at al., 2010; Johnson et al., 2011). Seizures do not always last beyond childhood, but there is evidence that pediatric epilepsy is associated with adverse long-term psychosocial outcomes, even in those who no longer have the condition (Shinnar & Pellock, 2002).

The number of AEDs a child receives is thought to impact their developmental and cognitive functioning (Elger et al., 2004; Bulteau et al., 2000). As such, in our study, We have collected data including the number of AEDs a child was taking before their first clinic visit at the Royal University Hospital (RUH) and the number of AEDs they were prescribed across the history of their epilepsy.

2.6.2.1.2 Ketogenic diet

A ketogenic diet, also known as a high-fat and low-carbohydrate diet, is a therapeutic alternative that is often considered when an epileptic child is resistant to anti-epileptic drug (AED) therapy or parents choose to not treat their child with drugs (Greener, 2014). As with any change to a diet, this form of treatment can be difficult to introduce to the regimen of any individual and there are further challenges to regularly maintain the diet in a personally suitable way. Additionally, this form of the diet requires a fairly high level of support from health care specialists (Reading, 2010). However, this diet can be the right form of therapy for a child with a high frequency of seizures and it has proven to be an effective method for many epileptic children.

Ketogenic diets can involve a great deal of maintenance and monitoring, more than other treatment methods, for a family but are still a widely preferred method for patients have tried AEDs without success or do not want the drug intake to begin with. For those children who remain on the diet and achieve greater than a 50% reduction in seizures, a ketogenic diet is recommended to be continued for a minimum of two years, similarly to AEDs (Sharma & Jain, 2014). Ketogenic diets can either be weaned immediately in cases of emergency or more slowly over weeks or months by reducing the ratio gradually in those who have been treated for years (Sharma & Jain, 2014).

The efficacy of a ketogenic diet is better than most of the new AEDs and is more feasible for families without a drug plan (Sharma & Jain, 2014). It should be considered in patients with refractory epilepsy, after the failure of two or three appropriately attempted anti-epileptic

drugs (AEDs). However, in general, half the patients treated with a ketogenic diet will have at least a 50% reduction in the seizure frequency of child subjects with refractory epilepsy (Sharma & Jain, 2014). Since many patients find it difficult to maintain this diet, individuals usually opt to discontinue it if they do not experience any benefit. Ketogenic diets result in shorter or medium term benefits in seizure control, the effects of which are comparable to modern AEDs.

It has been suggested that developmental improvements of varying degrees can be witnessed from those individuals who follow a ketogenic diet (Zhu et al., 2015; Pulsifer, 2001). These developmental improvements include fundamental areas of functioning such as language use and gross motor movement.

2.6.2.1.3 Surgery

Surgery can be an effective method for treating epilepsy (Freitag & Tuxhorn, 2005; Jayalakshmi et al., 2014; Maehara & Shimizu, 2001; Sunaga et al., 2009). It involves a referral from the pediatric neurologist to the neurosurgeon. Surgery may be the best option for drug-resistant patients and individuals who are showing no improvement after changing to a ketogenic diet (Jayalakshmi et al., 2014). This treatment method is typically considered after two or three attempts of anti-epileptic drug (AED) treatment that show no improvement. Decades ago, surgery was not as readily considered an option for individuals and families but now with increasing modern technology, surgery is becoming a more readily used method of treatment for pediatric epilepsy. A major encouraging factor of this treatment method is that many individuals who undergo surgery are able to discontinue their intake of further AED medication.

Research suggests that surgery affects child development in a number of ways including in the ways of language development and verbal memory (Jayalakshmi et al., 2014). There is strong evidence of the decline of verbal memory as far in advance as up to two years after a left temporal lobectomy which improves with time (Alpherts et al., 2006). Studies demonstrate an improvement in motor function, regardless of whether epileptic episodes were no longer

experienced or whether seizure frequency of the patient had decreased (Beckung et al., 1994; Romanelli et al., 2001; Krsek et al., 2002). Further, other researchers have found motor deterioration to be a common risk of epilepsy surgery (Chassoux et al., 1999; Graveline et al., 1999). With all the risks and complications involved in epilepsy surgery, it has generally been concluded that about 70% of those who have this form of treatment eventually become seizure-free (Freitag & Tuxhorn, 2005; Jayalakshmi et al., 2014; Maehara & Shimizu, 2001; Sunaga et al., 2009).

2.7 Summary

In summary, pediatric epilepsy plays a significant role in how development is affected in a child with the illness. It can be assumed from the studies in this literature review that seizures experienced throughout childhood influence developmental delay in various ways and waiting times can further provoke these delays. Reducing waiting times for children who experience suspected seizures would help in reducing developmental problems of the developing brain. In order to perceive a full understanding of this issue, it is important to recognize the actual process of regression beginning from the stage of diagnosis throughout follow-up investigations. Taking all of these studies into account will provide an understanding of the process as a whole and will complement the understanding of social equity. Given the prevalence and incidence of pediatric epilepsy in Canada and Saskatchewan, waiting time is an important factor to consider when understanding the clinical course of a child who has epilepsy.

CHAPTER 3: METHODOLOGY

3.1 Overview

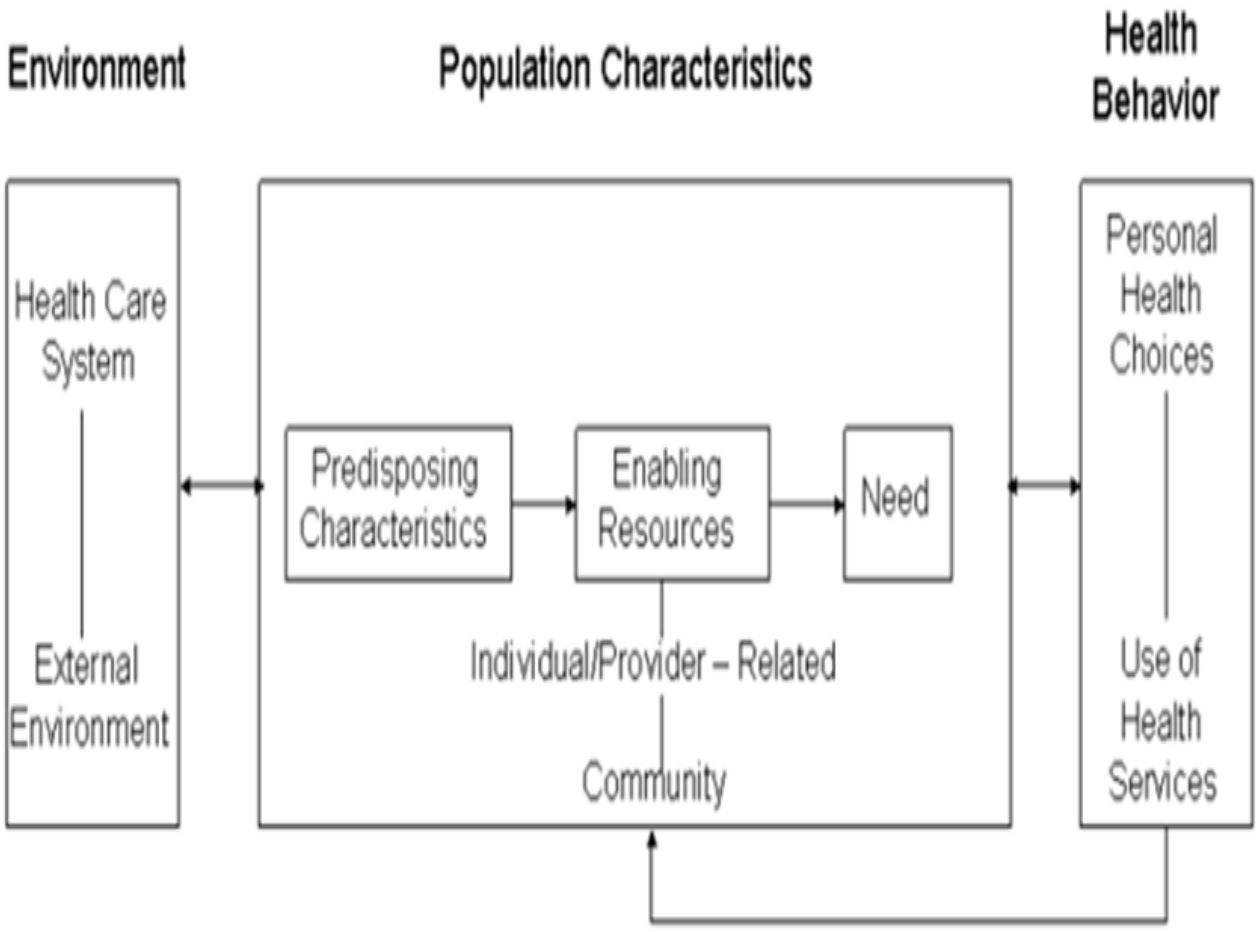
This chapter describes the conceptual model that will be used to guide this research. Data collection methods and procedures will also be discussed in this section. Characteristics of the participants, such as inclusion and exclusion criteria, and sampling considerations such as sampling scheme and sample size are reviewed in this section. The research design for the study is discussed, as well as the statistical analyses that will be conducted to address the research questions.

3.2 Theoretical perspective and conceptual model

This section provides a brief introduction into the theoretical perspective and conceptual model that will frame this study. The theoretical perspective provides information as to the ideology that explains health, while the conceptual model provides the operationalization of the theory for this study. The theoretical perspective that will be used to guide this research is a sociobehavioural or environmental perspective. This will help explain the use of health care services by taking social demographic factors, clinical factors, health management, health outcome (waiting time) and its impact on seizure outcome into account. Observing the interaction of these domains will be used to study access to the pediatric seizure clinic in this study.

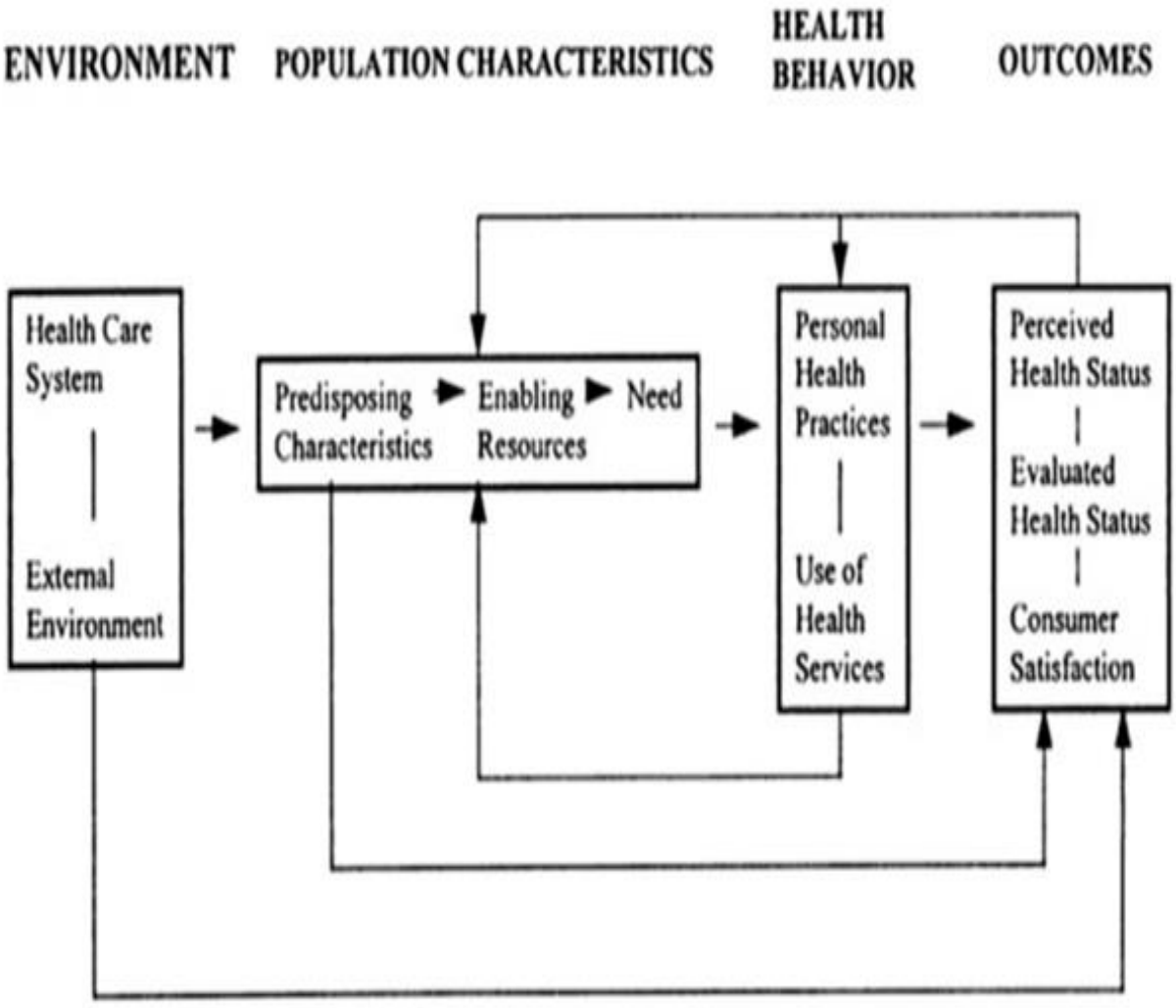
The development of the conceptual model of our study is exemplified in Figures 3.1 and 3.2. Figure 3.1 is the Andersen Model of Health Care Utilization (1995). Andersen's model displays environment, population characteristics, and health management as the three domains of importance in health care use. Environment includes the health care system and is interrelated with population characteristics which include predisposing characteristics, enabling resources, and need characteristics of the individuals using the health care services. Health management involves personal health choices as related to the use of health services and is also interrelated with population characteristics.

Figure 3.1: Andersen model of health care utilization (Andersen, 1995)



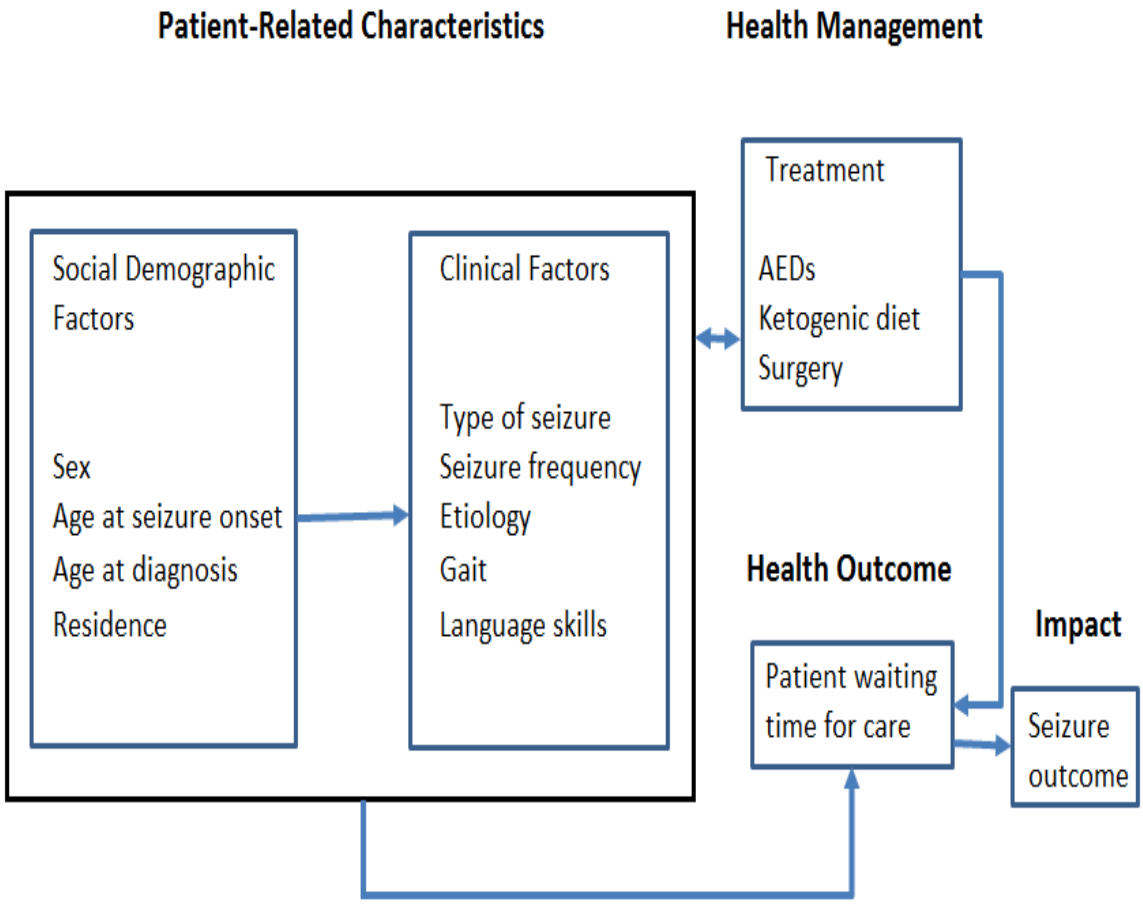
The Andersen Model of Health Care Utilization evolved into the Andersen Behavioral Model of Health Services Use (Figure 3.2). The evolved model includes health outcomes which we have included in our proposed conceptual model. This involves the perceived health status of individuals, their evaluated health status (usually by a health care practitioner), and consumer satisfaction.

Figure 3.2: Andersen behavioral model of health services use (Andersen, 1995)



In this study, the proposed conceptual model exemplified is shown in Figure 3.3 as an extension of Andersen's model.

Figure 3.3: Proposed conceptual model as modified Andersen behavioural model



Abbreviations: AEDs = anti-epileptic drugs

The model depicted in Figure 3.3 has been altered from Andersen's original model but still displays four main domains: patient-related characteristics (i)social demographic factors and ii) clinical factors), iii) health management, and iv) health outcome with the addition of impact. The interconnectedness between these factors will be assessed.

The social demographic factors of our study include the age at seizure onset, sex, the age that the child is at diagnosis, and residence which is either an urban or rural location in the province of Saskatchewan. The clinical factors of our study include the type of seizure the child experienced, etiology, the seizure frequency experienced, gait, and language skills. In our study, health management are the treatments available at the pediatric seizure clinic including: anti-epileptic drugs (AEDs), ketogenic diet, or surgery.

The health outcome in our study is waiting time and we are also interested in the impact this has on seizure outcome by looking at two possibilities of it: seizure-free - no longer having seizures at follow-up clinic appointments and not seizure-free - continuing to have seizures at follow-up clinic appointments. All of the main domains and factors within this depicted model work together in identifying the need for medical attention, understanding the treatment required, and the wait times leading up to the pediatric seizure clinic services.

3.3 Study design

This is a retrospective population-based study. Data collection consisted of data extraction from the medical charts of patients with pediatric epilepsy who attended the pediatric seizure clinic at the Royal University Hospital (RUH) in Saskatoon, Saskatchewan, Canada.

3.4 Inclusion/exclusion criteria

All children who visited the pediatric seizure clinic at the Royal University Hospital (RUH) from 2012-2015 were considered for this study. One child was not assessed for eligibility because they did not have health insurance and therefore, there was no way to link their record with the Saskatoon Health Region (SHR)'s electronic database. Inclusion and exclusion criteria that were considered in this study are summarized in this section. This particular time range (years 2012-2015) was chosen because those diagnosed more recently tended to have more complete

records in their medical charts and the electronic medical system was more widely used at the SHR during this time range.

3.5 Inclusion criteria

The inclusion criteria that were pertinent in the execution of this study included the following:

- Patients at the seizure clinic of Royal University Hospital located in Saskatoon, Saskatchewan;
- All patients with a first clinic appointment between January 1 2012 and December 31 2015;
- Patients diagnosed with partial or generalized seizures;
- A diagnosis of epilepsy confirmed by a pediatric neurologist;
- Age of child ≤17 years old at the time of the study;

3.6 Exclusion criteria

The exclusion criteria that were considered in the implementation of this study included the following:

- Children who were not diagnosed at the Royal University Hospital seizure clinic in Saskatoon;
- Children who were not diagnosed with epileptic seizures as determined by a pediatric neurologist;
- Children ≥ 18 years at the time of diagnosis; or
- Children who were seen for the first time before January 1st 2012 and after December 31st 2015

3.7 Sample, participants, and population

3.7.1 Study population

Saskatoon is the most populous urban center in the province, located in central Saskatchewan, Canada. Saskatoon's population is composed of 17.9% individuals under the age of 15 years (18.7% males and 17.2% females) and historically is one of the provinces in Canada with the youngest age demographics (Statistics Canada, 2012). The population under study in this research project consisted of children aged 0 – 17 years old residing within the province of Saskatchewan.

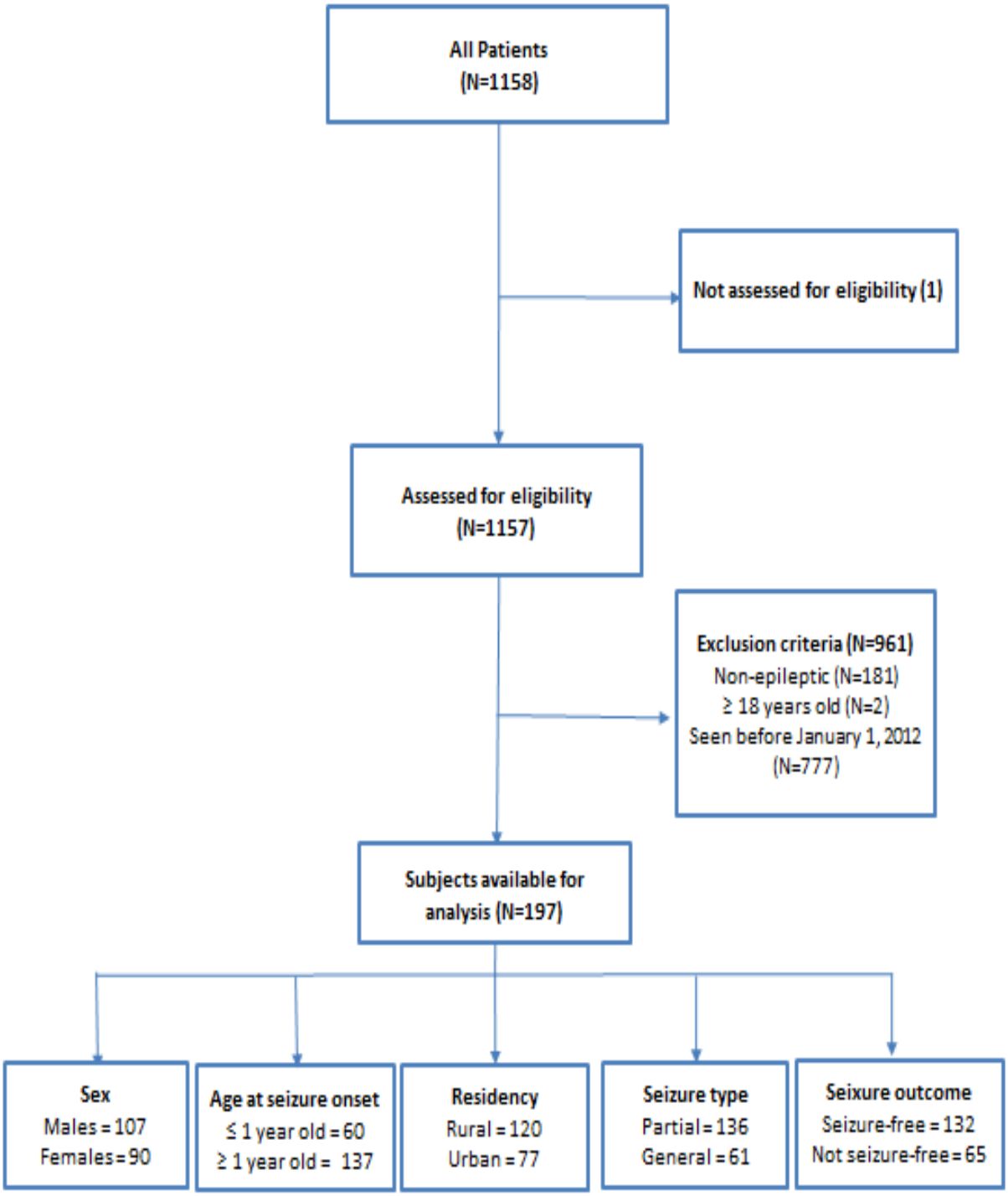
3.7.2 Sampling and participants

A convenient sampling scheme was used in this study because it was the most practical form of gathering participants since epilepsy is fairly low in incidence. The accessibility of participants due to geographical location was another reason for the recruitment of this pool. The population was pre-determined by the electronic health records database at the Saskatoon Health Region (SHR).

The Royal University Hospital (RUH), located in Saskatoon, is the only site in the province of Saskatchewan that is specialized in pediatric epilepsy care for individuals that are under 18 years old.

The sample for this study started with 1158 children, gathered from the Royal University Hospital (RUH) in Saskatoon, Saskatchewan. Each child included in this study had an appointment with a pediatric neurologist at the seizure clinic between January 1, 2012 and December 31, 2015. After considering all of the inclusion criteria, the sample size was 197 participants. A flow diagram of the patients that were considered for this study is illustrated in Figure 3.4.

Figure 3.4: Study flow diagram of epileptic patients seen between January 1, 2012 and December 31, 2015



3.8 Ethics approval

This study required approval by both the research ethics review boards of the SHR and the University of Saskatchewan since each of these boards partnered in making this research possible. Approval to carry out the study was obtained from the University of Saskatchewan (Bio # 15-238) research ethics review board. Permission to collect data was also obtained from the Saskatoon Health Region (SHR) research ethics review board. Approval processes for both organizations occurred in the final quarter of 2015.

3.9 Data collection statistical methods

3.9.1 Data collection

Data collection first began with those individuals who were diagnosed earliest in 2012 and was chronically collected forward up until the collection of those who were diagnosed in 2015. The measurement tool that we used to conduct this study was the electronic medical records of the Saskatoon Health Region (SHR). The data collected at this site was directly recorded into an excel dataset that was password-protected and saved on an encrypted USB device.

A total of 24 variables were taken into account during the analysis phase, according to the study hypothesis. Data items included information on demographics (age, sex, residence), epilepsy diagnosis data (date of epilepsy diagnosis), date of referral to the Royal University Hospital (RUH) seizure clinic, epilepsy presentation (seizure frequency, seizure type, symptoms experienced), past medical history (family, social, birth), epilepsy treatment, medical and neuro-imaging examinations (neurological examinations, MRI, and EEG readings).

3.9.2 Data collection variables

The independent variables that were analyzed in the course of this study are summarized in Table 3.2. A total of 17 variables were not included in the analysis either because they were believed to be irrelevant to the results, they had little analytical value for the study as they were not commonly documented from the clinical visits, or not enough cases had reported the information. Several of the variables that were collected were not consistently identified across the physicians onsite, thus many physicians did not record this information in their patient notes.

3.9.3 Variable selection

3.9.3.1 Independent variables

In order to perform this research and the analysis, a number of independent or causal variables were collected. These variables are listed in Table 3.2 and were selected to be incorporated based on the information that was available in the electronic medical records. The environment and population characteristics included variables that were either available regarding personal information or were available variables that were recorded by the pediatric neurologist at patient appointments.

Various baseline characteristics including social demographic factors, clinical factors, health management, health outcome, and impact of the sample are listed in Table 3.1. These characteristics include the age of participants, age at seizure onset, sex, residence, seizure type, etiology, development, waiting time, follow-up time at the pediatric seizure clinic, and seizure outcome.

Table 3.1: Baseline characteristics of study sample (N=197)

Variable	Mean (± SD); N (%)
Mean Age at Diagnosis (years)	6.2 (±5.2)
Mean Age of Seizure Onset (years)	5.60 (±5.1)
Female (%)	90 (46%)
Rural Location (%)	120 (61%)
Epilepsy Type	
Partial (%)	136 (69%)
Generalized (%)	61 (31%)
Etiology	
Unidentified	89 (45%)
Genetic	70 36%)
Structural	38 (19%)
Development	
Abnormal Gait	24 (12%)
Abnormal Language Skills	38 (19%)
Treatment	
Anti-epileptic Drugs	196 (99%)
Ketogenic Diet	21 (11%)
Surgery	7 (4%)
Mean Waiting Time (months)	4.33 (±3.6)
Mean Follow-Up Time (months)	20.9 (±11.0)
Seizure-free	132 (67%)

The independent variables used in this analysis are listed and summarized in Table 3.2. This list of variables was chosen as identified by the literature review and based on their influence towards waiting times.

Table 3.2: Independent variables used in data analysis

Category	Variable	Description	Type
Patient-related characteristics			
Social demographic factors			
	Age	At time of study	Continuous
	Sex	Male/Female	Categorical
	Age at seizure onset	At diagnosis	Continuous
	Residence	Name of residing city/town	Categorical
Clinical factors			
	Type of seizure(s)	Partial/General	Categorical
	Seizure frequency	0-99	Categorical
	Etiology identified at last visit	Yes/No	Categorical
	Etiology	Genetic/Structural/Unknown	Categorical
	Gait	Walk/Unable to walk	Categorical
	Language	Age appropriate/Not age appropriate	Categorical
Health management			
Treatment			
	Number of AEDs before first clinic	0-99	Categorical
	Number of AEDs historically	0-99	Categorical
	Surgery	Yes/No	Categorical
	Ketogenic diet	Yes/No	Categorical
	MRI results	Normal/Abnormal	Categorical
	Date of first EEG results	Date	Categorical
	EEG results	Normal/Abnormal	Categorical
	EEG telemetry performed	Yes/No	Categorical
Health outcome ***Waiting time***			
	Duration of waiting time	Number of months	Categorical
	Date of referral to seizure clinic	Date	Categorical
	Date of first clinic visit	Date	Categorical
	Number of clinic visits	0-99	Categorical
	Follow-up time	Number of months	Categorical
Impact ***Seizure outcome***			
	Seizure outcome	Seizure-free/not seizure-free	Categorical

3.9.3.2 Dependent variable

The outcome or dependent variable of interest in this study was waiting time. We were interested in how the period of time between a first seizure occurrence and a first clinic appointment impacts the seizure outcome. This variable was distributed into two distinguishable categories and it is defined in the following ways:

1) Seizure-free: the study participant experienced no further seizures as identified in the last six months and as identified by a pediatric neurologist on clinic follow-up appointments; and

2) Not seizure-free: the subject continued to experience seizures as confirmed by a pediatric neurologist after the subject's first clinic visit as identified at follow-up appointments.

3.9.4 Risk factors and protective factors for waiting time in pediatric epilepsy

There are a number of factors which can contribute to the clinical course of waiting time. This study focuses on risk factors and protective factors. Risk factors are elements that increase the risk or likelihood of an individual being affected by lengthened waiting times in pediatric epilepsy. Conversely, protective factors are those that reduce the likelihood of lengthened waiting times.

Risk factors can influence seizure outcomes in a number of ways. The more risks a child is exposed to, the greater the likelihood they will experience either lengthened waiting times in pediatric epilepsy or a less desirable seizure outcome. These risk factors include rural residency, young age at seizure onset (<1 year old), and development. Protective factors help in reducing the likelihood of lengthened waiting times and include such factors as urban residency, older age at onset and age-appropriate development.

3.9.5 Data analysis procedures

The data was cleaned by checking the distribution of variables. The data was also checked for potentially incorrect values during this process. The data was categorized based on the frequencies of variables.

3.9.6 Descriptive analysis

Descriptive statistics were computed using the information on population characteristics that was collected on patients who were eligible for analysis in our study. Descriptive data involved categorical data from patient-related characteristics such as the social demographic data (age, sex, residence) and the clinical characteristics (type of seizure, seizure frequency, etiology, etc.), summarized in frequencies, percentages and proportions. This analysis also included data from health management (treatment use), health outcome (waiting time), and the impact (seizure outcome).

3.10 Logistic regression analyses

Fixed covariates were the only variables included in the logistic regression models. Such covariates included environment, population characteristics, and health manamgent. Potential factors that were tested and included in the multivariate models include age diagnosis, age at seizure onset, sex, residency, type of seizure, waiting time, development (gait and language skills) and treatment use methods as was determined through the literature review.

The analysis of this study was intended to address the two objectives that were identified in the first chapter of this paper:

1) It characterized seizure outcomes for pediatric epilepsy in terms of the waiting time; and

2) It further identified any possible risk factors that were associated with waiting times that lead to seizure outcome by checking the interaction of variables that were observed

Logistic regression analysis was used in order to calculate adjusted Odds Ratios (AOR) and 95% Confidence Intervals (95% CI).

3.10.1 Odds ratio and 95% confidence interval

The odds ratio (OR) was calculated in the analysis to show how much more likely it is that someone who is exposed to the factor under study will continue to have epilepsy as compared to someone who is not exposed to the factor. According to the results, there were many factors that played a role in seizure outcome. These factors will be discussed in the sections that follow.

3.10.2 Univariate analysis

To control the effect of confounders, univariate analysis of variance which includes regression analysis was used for all variables that were found to have any significant differences to check for confounders.

Univariate logistic regression analysis techniques were utilized to examine the relationship between each predictor/potential risk factor as outlined in the literature review and the seizure outcome, whether the patient was seizure-free for a period within 6 months, 12 months, and 18 months. The purposeful selection process began by conducting a univariate analysis of each variable.

The level of significance that was used for tests of univariate logistic regression analyses were set to .05 ($\alpha = .05$).

3.10.3 Multivariate analysis

The multivariate model was built based on the values of the results that were calculated from running the univariate model analysis. All variables that were less than .20 from the univariate analyses were included in the multivariate models.

The multivariate logistic regression analysis was performed by adding each of the significant factors from the conceptual model to the model of analysis in order to see whether they were significantly associated with the seizure outcome of the child patients who were included in this study. The significance of these results was then calculated to determine factors of collective value in our study.

The level of significance used to perform the multivariate logistic regression analyses was set to .05.

3.10.4 Interaction

Interaction terms between seizure outcome and each of the significant covariates according to the multivariate logistic regression analyses were assessed. The level of significance for interaction terms was .05.

3.10.5 Software

Microsoft Excel was utilized to input all data collected through electronic medical chart review from the Saskatoon Health Region (SHR) database and all analyses were generated through the use of SPSS version 23.0 for this study.

CHAPTER 4: RESULTS

4.1 Overview

The analysis in this section was restricted to the 197 child participants with epilepsy that were involved in this study. The results described are addressed according to the four research questions.

4.2 Patient-related characteristics

Social demographic factors

The number of female subjects was 90 (46% of subjects) and the number of male subjects was 107 (54% of subjects).

The social demographic factors of this sample confirm that the mean age at seizure onset was 5.6 years old (SD=±5.0). The mean age at the time of diagnosis was 6.2 years (SD =±5.2).

The distribution of residence in this study shows that 61% of subjects lived in a rural environment (within the Saskatoon Health Region (SHR)) and 39% of subjects resided in an urban environment (outside of the SHR).

Clinical factors

In terms of the clinical presentation that subjects displayed at appointments, 31% of subjects had a general epilepsy presentation and 69% had a partial epilepsy presentation. All of the subjects were treated with clinical care at the seizure clinic in the Royal University Hospital of Saskatoon.

In terms of the seizure frequency experienced within the sample population, 26% presented with less than 10 seizures and 74% of subjects presented to the hospital with more than 10 seizures.

In terms of language and motor development, 12% of subjects presented with gait that was not age-level appropriate and 19% of subjects presented with language that was not age-level appropriate.

Health management - Treatment

In terms of the treatment sought, 95% of subjects were treated with anti-epileptic drugs (AEDs), 4% of subjects were treated with surgery, and 11% of subjects were treated with a ketogenic diet.

Amongst the sample population, the average number of clinic visits by patients at the Royal University Hospital (RUH)'s pediatric seizure clinic was 4.3 (±2.5) with the fewest number of visits being 1 and the most frequent number of visits being 24 throughout the clinical course of the patient.

The average follow-up time of those using the services at RUH's pediatric seizure clinic was 20.9 months (±11.0) with the 2.4 months as the shortest follow-up time and 54 months as the longest follow-up time.

Health outcome – Waiting time

The mean duration of waiting time for a first clinic appointment was 4.3 (±3.6) months. The range for waiting time that subjects experienced was between 0 months through 24 months.

Impact – Seizure outcome

At the last seizure assessment, 132 patients were identified as seizure-free and 65 patients were identified as not seizure-free.

4.2.1 Differences by seizure outcome

Descriptive analysis was performed to characterize the variables and their distributions in the data; these results are presented in Table 4.1 and categorized by seizure outcome. Additionally, p-value is displayed. The descriptive statistics were computed for all information on the eligible subjects that were used to complete this analysis.

Of the 65 that were classified as not being seizure-free, 54 (83%) experienced more than 10 seizures, while among the 132 seizure-free, 91 (69%) experienced more than 10 seizures (p=0.034).

Slightly more subjects that were not seizure-free experienced gait problems 13 (20%) when compared to those who were seizure-free 11(8%; p=0.018). Additionally, 19 (29%) of those who were not seizure-free experienced language difficulties while 19 (14%) of those who were seizure-free experienced language difficulties (p=0.013).

Subjects who were not seizure-free experienced had a mean waiting time of 3.5 months (SD=3.7) while subjects who were seizure-free had a mean waiting time of 4.7 months (SD=3.2). The data showed that there was a difference in waiting time between patients who were seizure-free and patients who were not seizure-free (p=0.018).

Table 4.1: Study characteristics stratified by seizure outcome (N=197)

	Seizure-free (n = 132)	Not seizure-free (n = 65)	p-value
Patient-related characteristics			
Social demographic factors			
Sex			.32
Male	74 (56%)	33 (51%)	
Female	58 (44%)	32 (49%)	
Residency			.42
Urban	49 (37%)	28 (43%)	
Rural	83 (63%)	37 (57%)	
Age at epilepsy onset, y	5.5 (±5.0)	6.1 (±5.0)	.43
Age at diagnosis, y	5.9 (± 5.1)	6.7 (±5.2)	.40
Clinical characteristics			
Seizure type			.97
Partial	90 (68%)	46 (71%)	
General	42 (32%)	19 (29%)	
Seizure Frequency			.03
<10	41 (31%)	11 (17%)	
>10	91 (69%)	54 (83%)	
Gait not age-appropriate	11 (8%)	13 (20%)	.02
Language not age-appropriate	19 (14%)	19 (29%)	.01
Etiology			.31
Unidentified	56 (42%)	33 (51%)	
Genetic	49 (37%)	21 (32%)	
Structural	27 (20%	11 (17%)	
Health management			
Treatment			
Number of AEDs			
Total	1.8 (±1.3)	1.9 (±1.3)	.34
Before first clinic	0.64 (±0.7)	0.52 (±0.8)	.38
Surgery	6 (5%)	1 (2%)	.29
Ketogenic Diet	13 (10%)	8 (12%)	.60
Health outcome			
Waiting time			
Mean number of visits	4.3 (±2.2)	3.7 (±1.6)	.39
Mean waiting time, m	3.5 (±3.2)	4.7 (±3.7)	.01
Mean follow-up duration, m	20.9 (±10.0)	20.2 (±12.5)	.86

4.2.2 Differences by residence

Descriptive analysis was performed to characterize the variables and their distributions in the data; these results are presented in Table 4.2 and categorized by residence. Additionally, p-value is displayed. The descriptive statistics were computed for all information on the eligible subjects that were used to complete this analysis.

Of the 77 that were from a rural residence, 5 (6%) had language difficulties whereas 33 (28%) of the 120 subjects from an urban residence had a language difficulty. The data showed there was a difference between rural and urban residents in language difficulty ($p < .0001$).

Of the rural residents, the mean number of anti-epileptic drugs (AEDs) before the first clinic was 0.4 (SD=0.7) whereas the mean number of AEDs for urban residents was 0.7 (SD=0.8). The data showed a difference between rural and urban residents in number of anti-epileptic drugs taken before the first clinic visit ($p<0.001$).

The mean waiting time for rural residents was 5.5 months (SD=3.7). Urban residents had a significantly shorter mean waiting time of 3.6 months (SD=3.0). The data showed a difference between rural and urban residents in waiting time ($p < .0001$).

Table 4.2: Study characteristics stratified by residence (N=197)

	Urban (n = 120)	Rural (n = 77)	p-value
Patient-related characteristics			
Social demographic factors			0.35
Sex			
Male	62 (47%)	45 (69%)	
Female	58 (44%)	32 (49%)	
Age at epilepsy onset, y	5.6 (±5.1)	6.3 (±4.9)	0.9
Age at diagnosis, y	6.7 (± 5.0)	7.0 (±5.2)	0.86
Clinical characteristics			0.21
Seizure type			
Partial	77 (58%)	56 (86%)	
General	43 (33%)	21 (32%)	
Seizure Frequency			0.92
<10	32 (24%)	20 (31%)	
>10	88 (67%)	57 (88%)	
Gait not age-appropriate	19 (16%)	5 (6%)	0.05
Language not age-appropriate	33 (28%)	5 (6%)	<.0001
Etiology			0.56
Unidentified	52 (43%)	37 (48%)	
Genetic	44 (37%)	26 (34%)	
Structural	24 (20%)	14 (18%)	
Health management			
Treatment			
Number of AEDs			
Total	2.0 (±1.2)	1.7 (±1.3)	0.06
Before first clinic	0.7 (± 0.8)	0.4 (±0.7)	<.0001
Surgery	6 (5%)	1 (1%)	0.17
Ketogenic Diet	15 (13%)	6 (8%)	0.3
Health outcome			
Waiting time	4.4 (±2.8)	4.2 (±1.9)	0.41
Mean number of visits			
Mean waiting time, m	3.6 (±3.0)	5.5 (±3.7)	<.0001
Mean follow-up duration, m	20.9 (±11.0)	21.0 (±11.0)	0.99
Impact			
Seizure outcome			0.42
Seizure-free	49 (37%)	28 (43%)	
Not seizure-free	83 (63%)	37 (57%)	

4.2.3 Differences by motor development

Descriptive analysis was performed to characterize the variables and their distributions in the data; these results are presented in Table 4.3 and categorized by abnormal or normal motor development. Additionally, p-value is displayed. The descriptive statistics were computed for all information on the eligible subjects that were used to complete this analysis.

Of the 24 subjects who did not have age-appropriate motor development, 15 (63%) were also behind in language development.

Table 4.3: Study characteristics stratified by motor development (N=197)

	Age-appropriate (n = 173)	Not age-appropriate (n = 24)	p-value
Patient-related characteristics			
Social demographic factors			
Sex			0.39
Male	92 (53%)	15 (63%)	
Female	81 (47%)	9 (38%)	
Residence			0.05
Urban	101 (58%)	19 (79%)	
Rural	72 (42%)	5 (21%)	
Age at epilepsy onset, y	5.9 (±5.0)	5.3 (±4.9)	0.50
Age at diagnosis, y	6.8 (±5.0)	6.5 (±5.0)	0.94
Clinical characteristics			
Seizure type			0.05
Partial	121 (70%)	12 (50%)	
General	52 (30%)	12 (50%)	
Seizure Frequency			0.41
<10	44 (25%)	8 (33%)	
>10	129 (75%)	16 (67%)	
Language not age-appropriate	23 (13%)	15 (63%)	<.0001
Etiology			0.14
Unidentified	82 (47%)	7 (29%)	
Genetic	59 (34%)	11 (46%)	
Structural	32 (19%)	6 (25%)	
Health management			
Treatment			
Number of AEDs			
Total	2.0 (±1.3)	1.6 (±0.7)	0.13
Before first clinic	0.6 (±0.8)	0.4 (±0.6)	0.24
Surgery	7 (4%)	0 (0%)	0.32
Ketogenic Diet	18 (10%)	3 (0%)	0.76
Health outcome			
Waiting time	4.3 (±2.6)	3.8 (±1.6)	0.71
Mean number of visits			
Mean waiting time, m	4.4 (±3.5)	4.5 (±2.7)	0.54
Mean follow-up duration, m	20.5 (±20.5)	23.7 (±14.2)	0.12
Seizure outcome			0.02
Seizure-free	49 (37%)	28 (43%)	
Not seizure-free	83 (63%)	37 (57%)	

4.2.4 Differences by language development

Descriptive analysis was performed to characterize the variables and their distributions in the data; these results are presented in Table 4.3 and categorized by language development. Additionally, p-value is displayed. The descriptive statistics were computed for all information on the eligible subjects that were used to complete this analysis.

Of the 38 that experienced language difficulties, 27 (71%) were male while 11 (29%) were female. The data showed that there were differences between those that were age-appropriate and not age-appropriate in males and females (p=0.021).

Table 4.4: Study characteristics stratified language development (N=197)

	Age-appropriate (n = 159)	Not age-appropriate (n = 38)	p-value
Patient-related characteristics			
Social demographic factors			
Sex			0.02
Male	80 (50%)	27 (71%)	
Female	79 (50%)	11 (29%)	
Residency			<.0001
Urban	87 (55%)	33 (87%)	
Rural	72 (45%)	5 (13%)	
Age at epilepsy onset, y	6.0 (±5.1)	4.7 (±4.8)	0.24
Age at diagnosis, y	6.6 (±5.2)	5.6 (±5.0)	0.12
Clinical characteristics			
Seizure type			0.07
Partial	112 (70%)	21 (55%)	
General	47 (30%)	17 (45%)	
Seizure Frequency			0.22
<10	45 (28%)	7 (18%)	
>10	114 (72%)	31 (82%)	
Gait not age-appropriate	23 (13%)	15 (63%)	<.0001
Etiology			0.50
Unidentified	74 (47%)	15 (39%)	
Genetic	55 (35%)	15 (39%)	
Structural	30 (18%)	8 (22%)	
Health management			
Treatment			
Number of AEDs			
Total	1.9 (±1.3)	0.6 (±0.8)	0.95
Before first clinic	1.8 (±1.1)	0.6 (±0.6)	0.58
Surgery	6 (4%)	1 (3%)	0.73
Ketogenic Diet	17 (11%)	4 (11%)	0.98
Health outcome			
Waiting time	4.4 (±2.7)	4.0 (±1.5)	
Mean number of visits			0.37
Mean waiting time, m	4.4 (±3.5)	3.9 (±2.8)	0.36
Mean follow-up duration, m	20.9 (±11.0)	20.6 (±11.1)	0.83
Seizure outcome			0.02
Seizure-free	49 (37%)	28 (43%)	
Not seizure-free	83 (63%)	37 (57%)	

4.2.5 Differences by sex

Descriptive analysis was performed to characterize the variables and their distributions in the data; these results are presented in Table 4.5 and categorized by sex. P-value displays the significance of the covariate. The descriptive statistics were computed for all subjects based on the information available.

Of the 91 child patients that were female, the mean number of anti-epileptic drugs (AEDs) was 1.7 (SD=1.1) whereas the mean AEDs for males was 2.1 (SD=1.4). The data showed that there were differences in the total number of AEDs between males and females (p=0.05).

Of the females included, 4 child patients (4%) had surgery whereas 2 (2%) of males had surgery (p=0.07).

Table 4.5: Study characteristics stratified by sex (N=197)

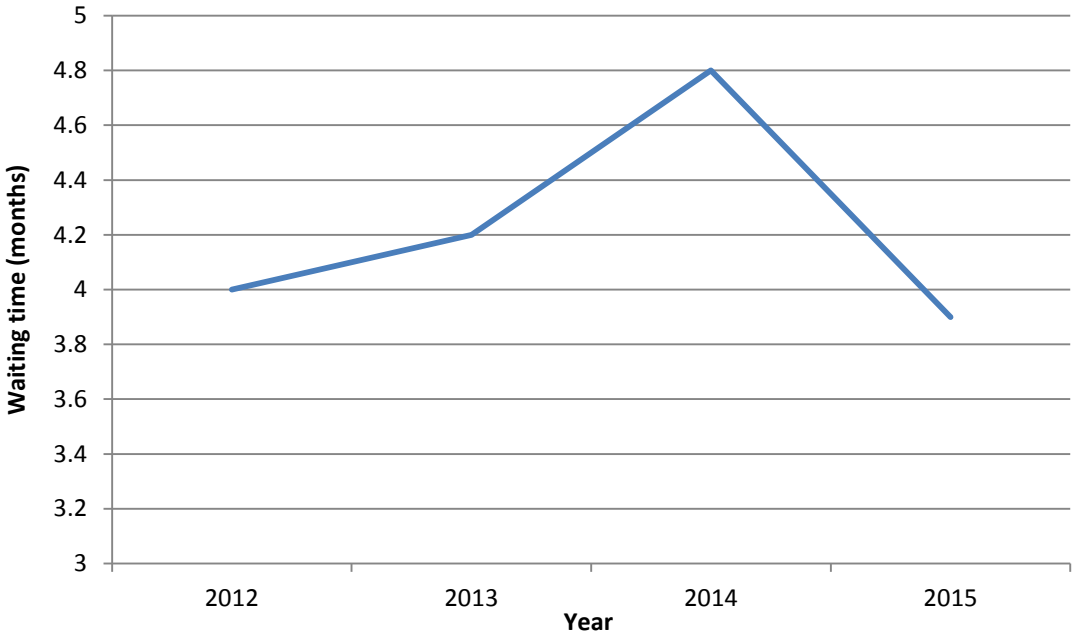
	Male (n = 132)	Female (n = 65)	p-value
Patient-related characteristics			
Social demographic factors			
Residency			0.65
Urban	63 (59%)	57 (63%)	
Rural	43 (41%)	34 (37%)	
Age at epilepsy onset, y	6.2 (±5.1)	5.8 (±4.9)	0.23
Age at diagnosis, y	8.9 (± 6.2)	9.0 (±4.7)	0.59
Clinical characteristics			0.8
Seizure type			
Partial	74 (70%)	59 (65%)	
General	32 (30%)	32 (35%)	
Seizure Frequency			0.59
<10	23 (22%)	29 (32%)	
>10	83 (78%)	62 (68%)	
Gait not age-appropriate	13 (12%)	11 (12%)	0.98
Language not age-appropriate	25 (24%)	13 (14%)	0.54
Etiology			0.95
Unidentified	46 (43%)	43 (47%)	
Genetic	40 (38%)	30 (33%)	
Structural	20 (19%)	18 (20%)	
Health management			
Treatment			
Number of AEDs			
Total	2.1 (±1.4)	1.7 (±1.1)	0.05
Before first clinic	0.58 (±0.7)	0.60 (±0.8)	0.86
Surgery	2 (2%)	4 (4%)	0.07
Ketogenic Diet	12 (11%)	9 (10%)	0.75
Health outcome			
Waiting time	4.3 (±2.5)	4.4 (±2.5)	0.84
Mean number of visits			
Mean waiting time, m	4.5 (±4.1)	4.4 (±3.3)	0.8
Mean follow-up duration, m	20.2 (±10.6)	21.8 (±11.4)	0.31
Seizure outcome			0.55
Seizure-free	73 (69%)	59 (65%)	
Not seizure-free	33 (31%)	32 (35%)	

4.2.6 Waiting time

Figure 4.1 below displays the waiting time experienced by pediatric epilepsy patients who attended the seizure clinic for diagnosis between 2012 and 2015.

Although there was a rise in the average waiting time in 2014, the number of patients also doubled from 2012. The number of pediatric neurologists steadily increased from 1 to 4 within the study period. In 2015, the shortest waiting times were observed and the clinic was staffed with the highest number of pediatric neurologists within the study period.

Figure 4.1: Waiting time at pediatric seizure clinic from 2012-2015 (N=197)



Number of Pediatric Neurologists:	1	2	3	4
Number of Patients:	28	50	65	54

4.3 Logistic regression

Logistic regression models were performed to identify the independent determinants of seizure outcome. All predictor variables analyzed were used as predictors in the logistic regression model. These included covariates from the conceptual model: external environment, population characteristics, health management, health outcome, and impact. Univariate models and a multivariate model with interactions were included.

4.3.1 Univariate logistic regression

Table 4.6: Univariate logistic regression results for prediction of seizure outcome within 6 months (N=197)

Variable	OR	95% CI	p-value
Sex			
Male	1		
Female	1.14	0.65 - 2.00	0.65
Age at seizure onset	1.01	0.95-1.07	0.79
Age at diagnosis	1.03	0.51-1.09	0.34
Residence			
Urban	1		
Rural	1.39	0.78-2.47	0.26
Gait			
Age-appropriate	1		
Not age-appropriate	2.96	1.17-7.50	0.02
Language skills			
Age-appropriate	1		
Not age-appropriate	2.13	1.02-4.41	0.04
Type of epilepsy			
Partial	1		
General	0.70	0.38-1.27	0.24
Etiology			
Unidentified	1		
Genetic	0.80	0.36-1.75	0.57
Structural	1.02	0.48-2.19	0.95
Number of AEDs before first clinic	0.92	0.65-1.32	0.66
Total number of AEDs	1.09	0.87-1.37	0.45
EEG	0.65	0.36-1.19	0.16
Ketogenic diet	1.50	0.60-3.73	0.39
Surgery	1.45	0.32-6.66	0.63
Number of visits	0.95	0.84-1.07	0.37
Duration of follow-up visits (months)	1.02	0.99-1.04	0.22
Waiting time (months)	1.12	1.04-1.22	0.01

OR = odds ratio; CI = confidence interval

Univariate logistic regression at 6 months showed that gait, language, and waiting time were statistically significant ($p<0.05$). Children with a gait that was not age-appropriate were 2.96 (95% CI: 1.17-7.50; p-value = 0.02) times higher odds of seizure in comparison to children whose gait was age-appropriate. Children with language that was not age-appropriate were 2.13 (95% CI: 1.02-4.41; p-value = 0.04) times more likely to have higher odds of seizure in comparison to children whose language was age-appropriate. Similarly, the analysis showed that waiting time per 1-month increase (OR=1.12; 95%CI, 1.04-1.22; p-value = 0.01) was associated with higher odds of seizure.

Table 4.7: Univariate logistic regression results for prediction of seizure outcome within 12 months (N=197)

Variable	OR	95% CI	p-value
Sex			
Male	1		
Female	1.16	0.65-2.07	0.61
Age at seizure onset	0.98	0.93-1.04	0.58
Age at diagnosis	0.99	0.94-1.06	0.96
Residence			
Urban	1		
Rural	1.52	0.85-2.74	0.16
Gait			
Age-appropriate	1		
Not age-appropriate	2.57	1.08-6.13	0.03
Language skills			
Age-appropriate	1		
Not age-appropriate	2.10	1.03-4.30	0.04
Type of epilepsy			
Partial	1		
General	0.79	0.43-1.47	0.46
Etiology			
Unidentified	1		
Genetic	0.67	.30-1.52	0.34
Structural	0.93	0.43-2.02	0.86
Number of AEDs before first clinic	0.98	0.68-1.41	0.92
Total number of AEDs	1.17	0.93-1.47	0.17
EEG	1.22	0.65-2.27	0.53
Ketogenic diet	1.55	0.63-3.86	0.34
Surgery	2.24	0.49-10.27	0.30
Number of visits	1.01	0.90-1.13	0.92
Duration of follow-up visits (months)	1.01	0.99-1.04	0.40
Waiting time (months)	1.08	1.00-1.17	0.05

OR = odds ratio; CI = confidence interval

In the univariate logistic regression analysis at 12 months, gait, language, and waiting time were statistically significant ($p<0.05$). Children with a gait that was not age-appropriate were 2.57 (95% CI: 1.08-6.13; p-value = 0.03) times higher odds of seizure in comparison to children whose gait was age-appropriate. Children with language that was not age-appropriate were 2.10 (95% CI: 1.03-4.30; p-value = 0.04) times higher odds of seizure in comparison to children whose language was age-appropriate. The analysis showed that waiting time per 1-month increase (OR=1.08; 95%CI, 1.00-1.17; p-value = 0.05) was associated with higher odds of seizure.

Table 4.8: Univariate logistic regression results for prediction of seizure outcome within 18 months (N=197)

Variable	OR	95% CI	p-value
Sex			
Male	1		
Female	1.04	0.63-2.05	0.68
Age at seizure onset	0.99	0.94-1.05	0.81
Age at diagnosis	1.01	0.95-1.07	0.81
Residence			
Urban	1		
Rural	1.43	0.79-2.61	0.24
Gait			
Age-appropriate	1		
Not age-appropriate	2.60	1.10-6.19	0.03
Language skills			
Age-appropriate	1		
Not age-appropriate	2.02	0.98-4.15	0.05
Type of epilepsy			
Partial	1		
General	1.30	0.70-2.43	0.41
Etiology			
Unidentified	1		
Genetic	0.99	0.42-2.32	0.99
Structural	1.28	0.57-2.86	0.55
Number of AEDs before first clinic	0.94	0.64-1.37	0.73
Total number of AEDs	1.27	1.00-1.60	0.05
EEG	1.61	0.84-3.11	0.16
Ketogenic diet	1.53	0.61-3.83	0.37
Surgery	1.48	0.32-6.80	0.62
Number of visits	1.00	0.89-1.13	0.99
Duration of Follow-up visits (months)	1.02	0.99-1.05	0.18
Waiting time (months)	1.09	1.01-1.18	0.04

OR = odds ratio; CI = confidence interval

Univariate logistic regression at 18 months showed that gait, language, total number of anti-epileptic drugs (AEDs), and waiting time were statistically significant ($p<0.05$). The univariate analysis showed that gait that was not age-appropriate were 2.60 (95% CI: 1.10-6.19; p-value =0.03) times higher odds of seizure. Language that was not age-appropriate had higher odds of seizure were 2.02 (95% CI: 0.98-4.15; p-value = 0.05) times higher odds of seizure. Per 1-AED increase in history, child patients had 27% (OR=1.27; 95% CI: 1.00-1.60; p-value = 0.05) higher odds of seizure. The waiting time per 1-month increase (OR=1.09; 95%CI, 1.01-1.18; p-value = 0.04) was associated with higher odds of seizure.

Table 4.9: Multivariate logistic regression results for prediction of seizure outcome within 6 months (N=197)

Variable	OR	95% CI	p-value
Gait			
Age-appropriate	1		
Not age-appropriate	3.15	1.22-8.13	0.02
Waiting time (months)	1.13	1.04-1.23	<0.001

OR = odds ratio; CI = confidence interval

In the multivariate analysis for 6 months seizure outcome, only gait and waiting time showed significant. Interaction between these two variables was examined but not significant. Thus, the final model for 6 month multivariate logistic regression showed that gait and waiting time in months were statistically significant factors in the analysis. A gait that was not age-appropriate had 3.15 (95% CI=1.22-8.13; p-value = 0.02) times higher odds of seizure when controlling for waiting time in months.

Table 4.10: Multivariate logistic regression results for prediction of seizure outcome within 12 months (N=197)

Variable	OR	95% CI	p-value
Gait			
Age-appropriate	1		
Not age-appropriate	2.66	1.11-6.42	0.03
Waiting time (months)	1.09	1.00-1.18	0.04

OR = odds ratio; CI = confidence interval

For the 12 month multivariate logistic regression analysis, gait and waiting time were statistically significant. Interaction between gait and waiting time was examined but not significant. A gait that was not age-appropriate associated with 2.66 (OR=2.66; 95% CI=1.11-6.42; p-value = 0.03) times higher odds of seizure, controlling for waiting time by number of months.

Table 4.11: Multivariate logistic regression results for prediction of seizure outcome within 18 months (N=197)

Variable	OR	95% CI	p-value
Gait			
Age-appropriate	1		
Not age-appropriate	3.1	1.25-7.70	0.02
Total number of AEDs	1.36	1.10-1.75	0.02
Waiting time (months)	1.11	1.02-1.20	0.02

OR = odds ratio; CI = confidence interval

18 months regression analysis showed that a gait that was not age-appropriate, total number of anti-epileptic drugs (AEDs) and waiting time were statistically significant. Interaction was examined between these three variables but found not significant. A gait that was not age-appropriate was associated with 3.10 (OR=3.1; 95% = 1.25-7.70; p-value = 0.02) times higher odds of seizure, controlling for total number of AEDs and waiting time.

CHAPTER 5: DISCUSSION

5.1 Summary of Findings

The main purpose of this study was to examine and describe relationships between waiting time and seizure outcome among children. The present study was conducted to explore which seizure-related variables were most significantly associated with seizure outcome in children with epilepsy.

A total of 1158 pediatric patients were included in this study held at the Royal University Hospital (RUH) in Saskatoon, Saskatchewan. Of those included in this sample, 378 (32.6%) child patients had a first seizure clinic assessment. Of the 378 child patients, 197 (52%) had epileptic events and were eligible for this study. 181 (48%) had non-epileptic events.

Waiting time

Our data showed an initial increase in waiting time as more patients attended the pediatric seizure clinic, however, in later years there was a decrease in waiting time as more pediatric neurologists staffed the clinic. The first research objective of this study was to identify if waiting time was associated with seizure outcome. There are very few studies that have observed waiting time in pediatric epilepsy. Determinants of waiting times in this study showed that seizure outcome associated with waiting time within 6 months, 12, months, and 18 months of

the seizure outcome in univariate and multivariate logistic analyses, respectively. Based on the descriptive analyses, child patients who had a seizure-free outcome waited an average of 3.5 months whereas child patients who did not have a seizure-free outcome waited an average of 4.7 months and showed to be statistically significant ($p = 0.01$). This finding is consistent with the results of other studies in which longer waiting times lead to higher odds of seizure (Berg et al., 2014; Luciano & Shorvon, 2007). Waiting time was also associated with residence where urban residents waited an average of 3.6 months and rural residents waited an average of 5.5 months and showed statistical significance ($p < .0001$). This is also comparable to previous studies that showed the same association with residential location (Guerrini, 2006; Kenney & Mann, 2003; Kozyrskyi & Prasad, 2004).

Based on the studies in this literature review and the analysis that resulted in this study, seizure outcome was strongly associated with having early access to the clinic. Unlike the studies in the literature review, the results of this study did not show a association with age at seizure onset or diagnosis. There was no indication that being less than a year old and being over 1 year old at seizure onset or diagnosis had any association with waiting time. The demographics were similar in terms of sex as there were more males than females diagnosed with epilepsy. This is similar to the demographic information of previous studies (Camfield et al., 1996; Kotsopoulos et al., 2002; Wirrell et al., 2011).

Recent studies showed that four factors played a role in delaying diagnosis including reasons from the parents, pediatrician, neurologist, and scheduling (Berg, 2014). It was not possible to collect this information in our study because this would have required interviewing the parents and care team after diagnosis which was not effective for a retrospective study. Berg (2014) also used a number of standardized intelligence tests to observe the differences in language and development. However, our study based the assessment of development on whether or not the child patient was age-appropriate according to the pediatric neurologist at the time of the clinical assessment.

Seizure outcome

The results of the multivariate analysis in our study looked at seizure outcome at 6 months, 12 months, and 18 months to compare the variables of significance at each of these stages in the clinical course. The models showed that gait and waiting time significantly associated with seizure outcome at all three stages of epilepsy. The total number of anti-epileptic drugs (AEDs) was not statistically significant until 18 months of the seizure outcome.

Our research objectives involved the identification of whether seizure outcome was associated with residence, gait, and language. Residence was not a predictor in any of the analyses for seizure outcome. Determinants of seizure outcome showed a difference of results for language when considered separately and when considered together. When considered separately, language did show up as a significant predictor in all univariate analyses but not in any multivariate analyses. Multivariate linear regression analysis of seizure frequency showed language that was not age-appropriate and general epilepsy type were significant.

Our findings on development are similar to other studies (Barnard & Wirrell, 1999; Karrash et al., 2017; Weiss et al., 2016). Our study significantly associated with gait both independently and when considered with other variables (p-value <0.05). Barnard and Wirrell (1999) found a association of neurodevelopmental delay in seizure patients although the number of children with developmental delay based on age was likely overestimated since milder delays may not have been clinically obvious to families. Our study confirms two parameters that the study by Barnard and Wirrell (1999) could not: i) their sample size was small with 52 child patients and ours was 197; and ii) there was only a 3-month follow-up which may have also overestimated the number of children with truly persistent new developmental delay whereas ours looked at seizure outcome up to 18 months. A separate study that found a association between seizure outcome and language followed participants with childhood-onset epilepsy for over 50 years and participants were given standardized tests (Karrash et al., 2017). Our study did not have this length of follow-up time, however, language showed to be independently significant at each 6 months (p-value = 0.04), 12 months, (p-value = 0.04), and 18 months (p-value = 0.05).

Our study showed that residence did not significantly associate with seizure outcome in the final models but as the descriptive statistics had represented, more rural residents were not seizure-free (57% or 37 out of 65 patients) than urban residents who were not seizure-free (43% or 28 out of 65 patients). In our study, residence was not traditionally assigned by population density within the province of Saskatchewan but rather was measured as being within the Saskatoon Health Region (urban) or beyond its borders (rural). A study in Manitoba found no statistically significant differences in prevalence rates of epilepsy between urban and rural populations of the province. However, a higher prevalence was found among children of all ages living in lower socioeconomic neighbourhoods in urban areas (Kozyrskyj et al., 2004). Our study did not collect information on parental income but did show higher prevalences of epilepsy amongst rural children. Another study looked at urban and rural settings for pediatric epilepsy and found a association with socioeconomic status (SES) (Abib et al., 2007). However, we did not collect this information in our study.

Age at onset was not found to be statistically significant in the multivariate analyses of our study as it was in the study conducted by Huang et al. (2014). Although, the cut-off age was less than 12 years old for Huang's (2014) study which may account for the difference in statistical significance since the cut-off age is 17 years old for our study and a considerable number of child patients were above the age of 12. Older age at onset predicts better prognosis in sporadic non-lesional temporal lobe epilepsy (TLE) (Aguglia, 2011). However, our finding is more in line with studies that included patients with a wider age range that did not demonstrate a consistent effect of age at onset on prognosis (Annegers, 1979; MacDonald, 2000). Our finding is also similar to multivariate analyses of predictive factors in children that have found no independent association of age at onset with diagnosis (Berg, 2001).

This study supports a association of the number of total anti-epileptic drugs (AEDs) consumed was significantly associated with seizure outcome (p-value = 0.02) which is consistent with prior studies (Teutonico, 2013). Through the use of multivariate statistics, Teutonico (2013) also indicated that consuming more than 3 AEDs along with a positive personal history, a presence of infantile spasms, as well as the use of stereoelectroencephalography (SEEG) resulted in a

poor seizure outcome for child patients with epilepsy. A meta-analysis showed an independent predictor of seizure recurrence in the last year of follow-up in pediatric epilepsy was also found to be the number of AEDs before withdrawal (Lamberink, 2017). This is more precisely consistent with our results that show significance at 18 months of seizure outcome but not at 12 months or 6 months. Previous studies documented a patient's response to the first AED as the strongest predictor of long-term seizure outcome in children (Dlugos et al., 2001; Kwan & Brodie, 2010; Schiller & Najjar, 2008; Sillanpää, 1993). Patients with AED treatment have also experienced drug resistance due to genetic or environmental factors (Johnson et al., 2011).

5.2 Study Strengths and Limitations

5.2.1 Strengths

There are three main strengths that this study is built upon. These involve aspects of the sample and data collection.

One strength is the presence of central care as all care is provided by the same pediatric epilepsy clinic in Saskatchewan. This allowed for a better sense of the clinical pathway with all patients going through the same administrative and clinical processes. This also allowed for representation of the province and allowed for the inclusion of a large population sample since all referrals must go through the Saskatoon Health Region (SHR), making it simpler to generalize to the province and therefore explore the variable of residency.

Another notable strength is that this study was a cohort study which makes it easier to draw causal association. Non-observational studies such as those with a cross-sectional design do not allow for this advantage.

A third strength of this study is the homogeneity of the population since this focuses on only children (individuals 17 years old and younger) who have had partial or generalized seizures

and who were seen by a pediatric neurologist at the Royal University Hospital in Saskatoon between the years 2012 and 2015.

5.2.2 Limitations

There are a number of limitations and potential biases to consider in this study involving the design and sample.

One limitation is that the study design is retrospective which limits the information that can be collected. Additionally, not all physicians consistently collected the same information during appointments with their patients. A prospective study or an interview with the patients would have limited this bias and would have been more representative of accurate reporting. Retrospective case ascertainment is a potential source of bias in that identifying cases for inclusion in the study may depend on unfavourable outcomes, as those who experience recurrence will be easier to identify than those who remain seizure-free after a second or third seizure. It is also more likely that patients with prospective recruitment are more comprehensively assessed for clinical variables and history of previous seizures at the point of diagnosis, thereby avoiding under- or over-estimation of the seizure frequency before the clinical presentation.

Another limitation of this study is that many physicians may not have referred their patient to the Saskatoon Health Region (SHR) pediatric neurology clinic or they may have misdiagnosed symptoms which would cause a bias in the sample size. The sample size was acceptable, and one physician would have preferred to obtain a larger number of participants. However, the researcher had a rather small pool from which to draw the sample given the specific inclusion and exclusion criterion. The SHR electronic medical records (EMR) were first in use in 2012 amongst practicing physicians and as time passed EMRs were updated more frequently and were more detailed. Thus, with the small sample size, the ideal statistical procedures were not carried out because statistical significance may not have been ascertained. Given the sample

size obtained in this study, results should be interpreted with some caution as a larger sample size of patients diagnosed with epilepsy may have generated a contrast of results.

Geographic location, especially proximity to an epilepsy center, may impact access to specialty care. Defining proximity to an epilepsy center, at the city- or township-level, is somewhat simplified especially for areas of Saskatchewan where regions within the province are large in terms of land mass. More detailed geographic data of the patient characteristics, such as address or postal code, would allow for better measurement of proximity. Nonetheless, this study provides valuable information that the impact of geography on access in seizure clinic services deserves further assessment.

These limitations to the design and sample would have required more time for modification. Although prospective studies are strong designs for drawing causality, they are difficult to conduct over a short range of time. Also, the misdiagnosis of symptoms is an element of practice that would be a challenge to control. Though limitations are present, the conclusion that lengthened waiting times in pediatric epilepsy is associated with significantly increased odds of having seizure is still believed to be associated.

5.3 Future Research Directions

More research is required to support these findings and to clearly determine the mechanisms by which waiting times are affected. Further prospective studies and larger cohorts would be beneficial in providing causal explanations of the effects of waiting time in pediatric seizure clinics.

The issues described in this study are not only concerning for the individual diagnosed with epilepsy, but they can also illustrate an economic burden for Saskatchewan. Between 2012 and 2015, one practicing pediatric neurologist joined the clinic in each subsequent year, totalling four specialists by 2015. In order to minimize issue such as access, engagement, and retention

of patients, a considerable health care cost may provide assistance for the province. Waiting time highlights the need to have early intervention available for these particularly vulnerable populations and intervene in the progression of pediatric epilepsy. The economic burden of early diagnosis is likely to be substantial for Saskatchewan and may be an expense that is not possible to accommodate.

Additionally, it would be of great value to reassess the variables observed here and other variables in a study population with a longer follow-up period. While certain variables may have short-term consequences, in order to identify factors which may only be evident over a longer period of time, a longer follow-up period or a longitudinal study would be required. The observation of this would allow for a more comprehensive causal relationship between the risk factors of seizure outcome and the clinical course experienced by patients with pediatric epilepsy.

As many risk factors as possible (where information was available) were considered for accessing a seizure clinic after a first seizure. Some factors need to be further explored. For example, availability of physicians was shown to be a factor for lengthened waiting times in the literature review but this information was not available for the purpose of the current study. During data collection, it was found that not all physicians recorded the reasons for cancelled or delayed appointments, whether it was due to the parent's schedule, the child's schedule, or the physician's schedule, but this could potentially be a relevant factor to consider in future studies on this subject.

The work conducted over the course of this dissertation has addressed several gaps in knowledge, including estimating the pooled prevalence of waiting time in persons with pediatric epilepsy and describing the patterns of waiting times in persons with epilepsy. Despite the knowledge available, the present identification and management of epilepsy continues to be less than ideal; by building upon the results of this work, progress can be made for the care of persons with epilepsy.

5.4 Summary

The results of this study do not differ much from other studies; however, it provides a more comprehensive view of pediatric epilepsy. Identification of factors influencing pediatric seizure outcome is vital to effectively care for patients and to improve their quality of life. In this study, it was found that gait, number of anti-epileptic drugs (AEDs), and waiting time were significant predictors of seizure outcome. This study highlights the need for increased testing and early detection, dedicated resources for clinical care, and treatment access. Moreover, this study calls for continued research on understanding the mechanisms by which disparities exist among various populations with regards to epilepsy waiting times. These results could further increase the understanding of other health care inequalities amongst other marginalized populations.

CHAPTER 6: CONCLUSION

This study attempted to address multiple disparities amongst child patients who utilize pediatric seizure clinic services. It also attempted to increase the knowledge and understanding of the Saskatoon Health Region (SHR) and amongst stakeholders regarding the disparity and its complex determinants among Saskatchewan‘s epileptic children and their use of pediatric seizure clinic services. This study will inform appropriate interventions to reduce waiting times at the seizure clinic in Saskatoon and beyond by disseminating the summary of the results to community health leaders, government, hospital administrators, as well as staff and physicians at the SHR.

Physicians responsible for the care of epileptic children should be aware of the increased odds of seizures and visit patients appropriately. The findings from this study provide evidence that both demographic and clinical characteristics each serve as important determinants for access to the necessary pediatric epilepsy care.

This study confirms the increasing data about patient waiting times in pediatric epilepsy onset and to emphasize the importance of a clinic appointment with a pediatric neurologist after a child experiences their first unprovoked seizure event. The findings of this study have potentially significant implications for a more comprehensive understanding of pediatric medical care services early in the diagnosis of pediatric epilepsy as this will help to prevent further developmental interruption. Early intervention remains a goal but with fewer resources available in Saskatchewan when compared to other regions of the country, it also largely remains an issue.

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