CHARACTERIZING THE EPIDEMIOLOGY OF EPILEPSY IN SASKATCHEWAN, CANADA

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By

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Abstract

Background and objectives: There are few studies of the prevalence of epilepsy in Canada, and there is no available estimate of the incidence and mortality of epilepsy in all age groups in the Canadian population. This study aimed to measure the incidence, prevalence, mortality and the temporal trends for epilepsy in Saskatchewan between 2005 and 2010. **Methods:** The study used a population-based, retrospective cohort design with information from the Saskatchewan's Population Health Registry databases for the periods of January 01, 2005 to December 31, 2010. The study cohort included the covered entire population of Saskatchewan with the identification of patients with epilepsy based on ICD codes. The incidence rate, prevalence, and standardized mortality ratio of epilepsy were measured over a period of six years and annually between 2005 and 2010 and age-standardized with the 2006 Canadian population. **Results**: The crude cumulative incidence of epilepsy was 63 per 100,000 person-years (age-standardized rate 62 per 100,000 person-years). Age-specific incidence was highest in the 75-79 age group (133.5 person 100,000 person-years). There was a significant decrease in the incidence of epilepsy over the study period. The incidence in self-declared Registered Indians (RI) was 95 per 100,000 person-years (age-standardized rate 122 per 100,000 person-years). It was significantly higher than the general population in most of the age groups. The overall prevalence was 8.5 in 1,000 people (9 per 1,000 if age-standardized to the 2006 Canadian population) with a male prevalence of 9 and a female prevalence of 8.4 per 1,000 person-years. There was a significant increase in the prevalence over time. The age-specific prevalence was high in 15-19 age group, 35-39 age group, and 80-84 age group. The cumulative SMR for the total group was 2.45 (2.7 in males and 2.2 in females). Age-specific SMRs were highest in the 10-14 age group. There was no temporal change in the SMR over the study period. **Discussion**: The findings of this study are consistent with incidence, prevalence and mortality studies from developed countries. However, the decrease in the incidence

of epilepsy over time has been only seen previously in Nordic countries and needs more research.

Significance: This study was the first in Canada to measure the incidence and all-cause mortality of epilepsy in all age groups. It provides core indicators of public health and healthcare needs of patients with epilepsy in Saskatchewan and Canada.

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Author

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Dedication

There are a number of people without whom this thesis might not have been written, and to whom I am greatly indebted.

To God,

To my children, Guillermo and Isabelle Tellez-Hernandez without whom this thesis would have been completed one year earlier. I added to the role of mother, the competing demands of work, study and personal development; I hope one day you may understand.

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List of abbreviations

AAN	American Academy of Neurology
AED	Antiepileptic drugs
AES	American Epilepsy Society
CCHS	Canadian Community Health Survey
CI	Confidence Interval
CAI	Computer-assisted interviewing
CMA	Census Metropolitan Area
COPD	Chronic Obstructive Pulmonary Disease
EEG	Electroencephalogram
ER	Emergency Room
GTCS	Generalized Tonic-Clonic Seizures
ICD	International Classification of Diseases
ID	Incidence Density
IS	Infantile spasm
ILAE	International League Against Epilepsy
IR	Incidence rate
MRI	Magnetic Resonance Imaging

MS	Multiple Sclerosis
NPHS	National Population Health Survey
OHS	Ontario Health Survey
OR	Odds Ratio
PHRS	Person Health Registry System
PHB	Population Health Branch
PWE	Patient with epilepsy
RI	Self-declared Registered Indian
RR	Rate Ratio
SK	Saskatchewan
SMH	Saskatchewan Ministry of Health
SMR	Standardized Mortality Ratio
UK	The United Kingdom
YRS	Years

CHAPTER 1: INTRODUCTION

1.1 Background

Epilepsy is a common chronic medical and social disorder with unique characteristics. It is usually defined as a disease of the brain characterized by its predisposition to generate recurrent seizures (1). Epilepsy is one of the most prevalent neurological conditions affecting some 50 million people worldwide (2). Moreover, this disease knows no geographical, racial or social boundaries, affecting people irrespective of sex and age (3). Epilepsy explains 1% of the global burden of disease, where the burden of disease is determined by the number of productive life years lost as a result of disability or premature death (3). Accordingly, epilepsy's burden is similar to that of breast cancer in women and lung cancer in men (2).

To understand a disease like epilepsy, knowledge about its distribution in the populations and factors that influence or determine its distribution is critical (4,5). Epidemiology is the basic science of medicine which studies the distribution of the disease. Epidemiology uses mortality and morbidity rates such as disease incidence (number of new cases of epilepsy that occur during a defined period) and disease prevalence (the number of affected persons present in a population at the specific time) as core indicators of public health and healthcare needs of a population.

1.2 Statement of the problem

Epilepsy is one of the most common neurological disorders worldwide and responsible for 20.6 million disability-adjusted life years (DALYs) lost. Patients with epilepsy have increased health-care needs, premature death and decreased productivity, and also face stigma and discrimination as well as huge gaps in access to care (6,7). In Canada, the overall epidemiology of epilepsy has not been well characterized. Of the few studies that have examined the epidemiology of epilepsy, most have been impacted by methodological problems such as self-reported diagnosis

of epilepsy, limited age groups (8–14), and restricted syndromes (15–17). Furthermore, none of the available studies have measure the incidence rate, mortality, or temporal trends of epilepsy across all age groups. Also, it is highly probable that temporal trends in the epidemiology of epilepsy have changed in recent years as a result of updated diagnostic criteria, the increased use of technology such as the electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), and the establishment of epilepsy programs in Canada. Provincially, specific epidemiological data for the prevalence, incidence rate, and mortality of epilepsy are needed to allocate resources efficiently, and to develop new programs and interventions for patients with epilepsy in Saskatchewan.

1.3 Purpose and Objectives

The purpose of this study is to estimate the overall incidence rate, prevalence, and mortality of epilepsy in Saskatchewan, Canada. This study also seeks to describe temporal trends in the incidence and prevalence of epilepsy over a period of six years with respect to age, sex, urban setting and ethnicity (self-declared Registered Indian (RI) status).

The specific objectives are:

1. To measure the yearly crude and standardized incidence rate and prevalence of epilepsy in the general population from 2005 to 2010
2. To describe the incidence of epilepsy stratified by sex, age group, and in Registerer Indians
3. To estimate the Standardized Mortality Ratio (SMR) for epilepsy
4. To evaluate temporal trends in incidence, prevalence, and the SMR of epilepsy overa six-year period

1.4 Research questions

Specific issues which have a reasonable expectation of being answered from available data are indicated below:

Incidence and prevalence of Epilepsy

- What are the patterns and temporal trends of incidence and prevalence of epilepsy in Saskatchewan by year, age, sex, and RI status from 2005 to 2010?

Mortality of Epilepsy

- What is the yearly all-cause SMR in those with epilepsy compared to the general population in Saskatchewan from 2005-2010 period by age and sex?

CHAPTER 2: LITERATURE REVIEW

2.1 Epilepsy: an overview

Epilepsy is a brain disease characterized by the predisposition to recurrent and unpredictable epileptic seizures(1) and can have multiple etiologies. An epileptic seizure is an abnormal and excessive discharge of brain neurons involving abnormal hypersynchrony between them (18). Practically, epilepsy is defined as (1):

1. At least two unprovoked seizures occurring >24 h apart.
2. One unprovoked seizure with additional features accompanied with circumstances that increase the possibility of a recurrence of seizures such an epileptiform electroencephalogram (EEG) study or stroke lesion in an imaging study such as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT)).
3. Diagnosis of an epilepsy syndrome such as Dravet syndrome, childhood absence epilepsy or juvenile myoclonic epilepsy

Epilepsy is generally considered to be resolved in individuals who had an age-dependent epilepsy syndrome but are now past the applicable age, or in those individuals who have remained without a seizure throughout the last 10 years, with no anti-seizure medication throughout the last 5 years(1).

Specific seizures can be categorized by clinical elements (e.g., complex partial seizures and generalized tonic-clonic seizures), whereas epilepsy syndromes can likewise be categorized by type of seizure, the presence or absence of neurologic or developmental abnormalities, and EEG findings (19).

Epilepsy syndromes fall into two general classifications: generalized and partial (or localization-related) syndromes. In generalized epilepsies, the main type of seizures starts at the same time in both cerebral hemispheres. Most generalized epilepsies have a significant hereditary component and are associated with the normal neurologic function. On the other hand, in partial epilepsies, seizures start in one or more restricted foci, but may then spread to include the whole brain. Most partial epilepsies are thought to be the result of one or more brain injuries, although most of the cases the etiology is unknown (19).

Epilepsy is known in almost every culture and has been documented for thousands of years. Epilepsy may occur at any age (20) and affects around 50 million people worldwide. Unfortunately, in spite of its pervasiveness, frequent treatment failures, and poorly understood mechanisms, the condition receives moderately little research funding (21).

The historical backdrop of epilepsy was summarized by the neurologist Rajendra Kale who wrote:

"4,000 years of ignorance, superstition, and stigma followed by 100 years of knowledge, superstition, and stigma (22)*."*

Epilepsy affects all aspects of the life of a person, including safety, memory, cognition, and mood. Social aspects such as driving, employment, and stigma may profoundly affect overall functioning. People with epilepsy (PWE) have worse quality of life, family function, and social support than people with other chronic diseases (8,23). Finally, PWE's are high users of healthcare facilities including the emergency room, hospital in patient beds, psychologist/ psychiatric specialists, social workers, nursing services and other health professionals (8).

2.2 Epidemiology of Epilepsy

Epidemiology is the study of the distribution, determinants and natural history of a medical condition in a population (5). The epidemiology of epilepsy is largely based on descriptive and analytical studies, as very little experimental work has been carried out on humans for various reasons, including logistical and ethical. Despite epilepsy being amongst the most common serious neurological conditions, there are many gaps in our understanding of its epidemiology. These deficiencies are partly due to methodological problems and also due to the failure to take fully into account epilepsy's heterogeneous nature (24).

Epilepsy is distributed unequally around the world. These dissimilarities have been attributed to varying exposures to various environmental factors such as malaria, neurocysticercosis, and injuries (particularly road traffic and birth-related injuries). Epidemiologic patterns of epilepsy are affected by differences in socioeconomic factors such as medical infrastructure, availability of preventative health programs and available care (25). Another source of discrepancy might be variations in the definition of epilepsy and discrepant methods of case ascertainment. For example, in 2005, the practical clinical definition of epilepsy was amended. The new definition included the previous definition of two unprovoked seizures >24hr apart but also included two additional criteria: 1. One unprovoked seizure accompanied with circumstances that increase the possibility of a recurrence of seizures such an epileptiform EEG study or stroke lesion in an imaging study and 2. The diagnosis of a known epilepsy syndrome such as West or Lennox-Gaustaut syndrome (18). This broadened definition would be expected to result in an increased incidence and prevalence of epilepsy compared to previous prevalence data in the Canadian population.

2.2.1 Incidence of epilepsy in developed countries

There are relatively few population-based studies of the incidence of epilepsy. In developed countries, the overall cumulative incidence of epilepsy is thought to be around 50 per 100 000/person-years (range 40-70 per 100 000/person-years) (26,27). Industrialized countries seem remarkably consistent across geographic areas for at least the last two decades.

Age

Most of the studies that report the incidence of epilepsy have been conducted in specific age groups such as children (13,28–34), adults (35–42) and elderly (40,41,43,44). In general, the information is consistent with the incidence in population-based studies. Epilepsy most commonly has its onset at the extremes of life. In developed countries it follows a U-shaped distribution with high incidence in the first few months of life, much lower incidence after the first year of life and then the highest incidence in the elderly (45). Only 50% of the cases of epilepsy start in later childhood or adolescence (27).

In children, it is speculated that improvements in prenatal care with advances in neonatal monitoring units (36) as well as healthier lifestyles of expectant mothers (46) could explain decreases in incidence over the time.

The high incidence of epilepsy in elderly individuals is likely related to the presence of comorbid conditions, specifically cerebrovascular diseases. Indeed, epilepsy is related to all the pathological spectrum of cerebrovascular diseases (small-vessel to major arterial occlusion), although it is more likely to be associated with larger cortical hemorrhagic areas of infarction (47).

The elderly are also prone to other disorders associated with epilepsy such as non-vascular dementias, tumors (brain and metastases), trauma, infections, and metabolic disturbances (47), which might increase the overall prevalence with age.

Sex

In most population studies the incidence of epilepsy is between 1.1 and 1.5 times greater in males than in females (48,49). This difference appears to be due to many of the major risk factors for epilepsy (i.e., head injury, stroke, central nervous system infection) being more frequent in males. Although in most but not all incidence studies, sex-specific differences in incidence have not been statistically significant, the consistency of the male-to-female differences across studies suggests that this is a true finding (45).

Race

Most of the population incidence studies have been performed in very ethnically homogeneous populations. There are few studies exploring possible racial differences. One of these studies determined the incidence and prevalence of epilepsy among elderly (65 yrs. or older) Medicare beneficiaries in the United States. The authors found that the elderly population of Native Americans had a statistically lower incidence of epilepsy (1.1 per 1,000) compared with white beneficiaries (2.3 per 1,000) (50).

Elderly African-Americans patients had up to an eight-fold higher risk of epilepsy than their Caucasian counterparts. Also, they did not find any incident cases among the elderly Asian and Native American group (51). This may be a result of the small numbers of elderly Native Americans. Native Americans have been found to the lowest life expectancy rate of all group, with a life expectancy of 71 years, which is six years less than the life expectancy in the white (sic) population (52).

2.2.1.1 Canadian incidence of epilepsy studies

One of the few studies measuring the incidence of epilepsy in Canada was conducted by Camfield et al. This study measured the incidence of epilepsy among children between one month and 16 years in the province of Nova Scotia from 1977 to 1985 (13). The authors identified cases through electroencephalography (EEG), records assuming that all the children with two or more unprovoked seizures previously seen by a physician would have an EEG available. The authors gathered the details of each case from the hospital neurologist's chart, or by a phone call to the family doctor or the parent or patient. The age-specific incidence rates were higher in the first year of life (118 per 100,000) followed by a plateau between the age of one and ten years (46 per 100,000). After age ten the incidence decreased dramatically and approached that of adults. There were differences in the incidence of epilepsy by sex depending on the epilepsy type. Females had higher incidences of absence seizures, myoclonus, infantile spasm, tonic, a-kinetic drop episodes or atypical absence seizures, but there was no difference between females and males in generalized tonic-clonic seizures and partial or partial secondarily generalized seizures types.

There are two more Canadian studies measuring the incidence of seizures. One is the study by Ronen et al. This study estimated the incidence of neonatal seizures in all obstetric and neonatal units in Newfoundland from January 1, 1990, to December 31, 1994. The incidence of neonatal seizures was reported as 2.6 per 1,000 live births (10). However, it is important to note that neonatal seizures often have an acute cause (provoked seizures) which would eliminate them for the diagnosis of epilepsy. The second study is the study by Brna et al. (15) This study measured the incidence of infantile spasms (IS) in the provinces of Nova Scotia and Prince Edward Island from 1978 to 1998(15), using EEG records, discharge diagnosis (ICD codes), chart review and

previous cohort study of childhood epilepsy. The overall incidence of IS was found to be 30.7 per 100,000 live births with a higher incidence (not statistically significant) in males than females (15).

2.2.2 Temporal trends in the incidence of epilepsy

Few studies have examined variations in the rates of epilepsy over time. Secular changes in the incidence of epilepsy are critical to understanding, as they may clarify changes in risk factors or uncover changes in clinical practice such as modifications in definitions, improvement in technology for detection and treatment, or increased awareness of the disease. One of the few articles published on this matter is the study by Hauser et al. (36) in Rochester, USA. This study measured the incidence of epilepsy over a 50 year period and reported a 40% decrease in the incidence of epilepsy in children under ten years between the decades 1935-1944 and 1955-1964, but a doubling of the incidence in adults older than 60 years between 1974 and 1984 (36).

More recently, the study in Tonbridge's pediatric population (<20 years) by Cockerell et al. in 1995 found a decrease in the incidence of epilepsy from 152.4 per 100,000 person-years in the period 1974-83 to 60.9 per 100,000 person-years in the period 1984-93 (53).

Among adults in Sweden (> 17 years), Forsgren et al. identified an increase in the incidence of epilepsy from 34 per 100 000 people (in the period of 1985-1987) to 47- 56 per 100 000 people in the period of 1992-1994 (35), although there are no definitive explanations for these changes. Hauser et al. (36) speculate that these changes might be related to major advances in the diagnosis and treatment of epilepsy.

2.2.3 Prevalence of epilepsy in developed countries

Because cross-sectional studies are easier and cheaper to conduct there are many more prevalence studies of epilepsy than of incidence; indeed, prevalence studies have been carried out

in more than 25 countries in all five continents (34,48,49,53–84). Moreover, most studies which do provide data on incidence also report prevalence. In relatively unselected populations in developed countries, the prevalence of epilepsy is found to be between 4 and 10 per 1,000 persons (85).

Age-specific prevalence

Epilepsy is a disease that can begin at any time of life. The pattern of age distribution in the prevalence of epilepsy varies among different countries. In developed countries, the prevalence increase during adolescence tends to be stabilize in adulthood and increase with age after 50, with the highest prevalence occurring in the elderly (86,87).

2.2.2.1 Canadian studies in the prevalence of epilepsy

There have been two recent publications assessing the prevalence of epilepsy in the Canadian population. Wiebe et al. (1999) measured the prevalence of epilepsy based on the 1990 Ontario Health Survey (OHS). The OHS was a large-scale survey sponsored by the Ministry of Health which used a questionnaire administered to the residents of Ontario for the first time in 1990 and repeated in 1996-1997. The sampling procedure was through a multistage, stratified, geographic cluster design. Telephone numbers were generated and dialed using random digit dialing (RDD) to 30,000 residents of Ontario aged 12 and over. The 1990 survey contained two parts; one part was a 22-page interview with only one member of a randomly selected household and the second part was a 26-page self-completed questionnaire filled out by each member of the household 12 and older (88). This survey did not include persons living on Indian Reserves, Canadian Forces bases, those in extremely remote areas, residents of institutions or collective dwellings, homeless persons, and those without access to a telephone. The phone questionnaire

explored recent or current health problems, use of health services and demographic information. In this study, Wiebe et al. found a prevalence of self-reported epilepsy of 5.8 per 1,000 people (8).

Later on, Tellez-Zenteno et al. (2004) assessed the national and regional prevalence of self-reported epilepsy in Canada (9) by analyzing data from two cross-sectional national health surveys: The National Population Health Survey: Cycle 3 (NPHS) and the Canadian Community Health Survey: Cycle 1.1 (CCHS).

The National Population Health Survey collected information related to the health and socio-demographic related descriptors of the Canadian Population. The target population included all ages of household residents from all provinces who responded voluntarily to the survey. Residents of Indian Reserves, Canadian Forces Bases and remote areas in Quebec and Ontario were excluded (89).The interviews were conducted by telephone in 95% of the cases and 5% of the interviews were in person. All interviews were conducted between 1998 and 1999. Questions covered health status, use of health services, determinants of health, chronic conditions, and restrictions of activities as well as socio-demographic information.

The Canadian Community Health Survey was a biennial survey that collected information related to health status, health care utilization and health determinants in the population of 12 years and older living in the ten provinces and the three Canadian territories.

Using the information collected in these surveys, Tellez-Zenteno et al. found a general prevalence of self-reported epilepsy of 5.2 per 1,000 in NPHS (1998-1999) and 5.6 per 1,000 in CCHS (2000-2001) (9). The authors also found a higher prevalence of epilepsy in those at the lowest educational level, those with the lowest income, those unemployed in previous years and non-immigrants.

In general, epilepsy prevalence studies in Canada have been based on population-based general health surveys where epilepsy was not the main objective. Moreover, the presence of epilepsy was ascertained by self-report with only one question: “Do you have epilepsy?” This method may have a resulted in unreliable data because people are not always aware of, or truthful about their epilepsy (90).

Age-specific prevalence

Both the Ontario Health Survey and the National Population Health Survey data found a higher prevalence of epilepsy in older age groups. The youngest group aged 12-14 years had a prevalence between 4.4 and 5.7 per 1,000 people; individuals aged 25-44 years had a prevalence between 5.9 and 6 per 1,000 people, and the oldest group of >65 years had a prevalence between 6.9 and 7.2 per 1,000) (8,9).

Other studies measuring the prevalence of epilepsy in the Canadian population include those by Kozyrskyj et al. (91), Schiariti et al. (14) and Prasad et al.(12).

The first study from Kozyrskyj et al. in Manitoba (11) found a general prevalence of epilepsy of 4.7 per 1,000 among children under 19 years of age. This study showed a steady increase with age in the prevalence of epilepsy from 3.5 per 1,000 people in children under five years old to 7.2 per 1,000 children aged 15-19.

The study of Schiariti et al. in BC (14) found the prevalence of epilepsy in children under 19 years of age to be 5.5 per 1,000 people. This study found that the prevalence of epilepsy was 7 per 1,000 people in those 0-4 years and steadily decreased with age to 5.1 per 1,000 in the 15-19 years old group. In this study, the highest prevalence, (overall and specifically in the group of

infants and pre-schoolers), was thought to be related to a misclassification bias (febrile seizures misclassified with epilepsy) and the inclusion of First Nation children (14).

The third study by Prasad et al. found a prevalence of epilepsy among subjects from 0 to 13 years old was 4.03 per 1,000 for cycle 2 of the survey and among subjects from 0 to 15 years old the prevalence was 5.26 per 1,000 for cycle 3 of the national survey.

Sex

Four Canadian studies explored differences in sex (8,9,12,14), but just one of them found a statistically higher prevalence of epilepsy in male versus female children (M:F 6.45:4.00 per 1,000 children) (12).

Race

In British Columbia, Canada, a study using administrative databases found a high prevalence of epilepsy in those health regions with a higher proportion of First Nations people (35). Similarly, an analysis of administrative data in Alberta (Calgary Health Region) found that Aboriginals were more likely than non-aboriginals to visit the Emergency Room (ER) (OR=4.9, 95% CI 3.2-7.4) or be hospitalized (OR=2.9, 95% CI 2.0-4.3) for epilepsy (92).

In conclusion, epilepsy is very frequent and affects a very considerable number of people. There have been original Canadian studies concerning epidemiological data of epilepsy, but no recent studies measuring the incidence and prevalence of epilepsy in all the age groups. Furthermore, there is a lack of Canadian studies of temporal trends in epilepsy.

2.2.6 Mortality of epilepsy in developed countries

Mortality in people with epilepsy (PWE) has been an important research focus since the 1930's (93) .

Various different measures have been utilized to calculate mortality in epilepsy, but the standardized mortality ratio (SMR) is the most widely recognized measure used to look at differences in the rates of death between a population of individuals with epilepsy and the general population (94).

The causes of death in epilepsy may be classified into three groups: a) unrelated causes, b) related to an underlying disease, and c) epilepsy-related deaths. The unrelated causes can include for example, neoplasms outside the central nervous system, ischemic heart disease or pneumonia. Death related to an underlying disease include brain tumors, cerebrovascular disease, and cerebral infections. The epilepsy-related category includes deaths directly related to a seizure, treatment, and medications as well as status epilepticus, sudden unexpected death i9n epilepsy (SUDEP), suicides, trauma, burns, drowning, asphyxiation, aspiration and trauma (95).

In one systematic review of studies exploring all-causes of death in patients with epilepsy, it was found that individuals with epilepsy were between 1.6 to 4.1 times (SMR= 1.6- 4.1) more likely to die than individuals in the general population. The review also concluded that males with epilepsy had higher mortality rates than females (96) .

Age-specific mortality

Most studies have found an inverse relation between SMR and age for all causes of death in epilepsy. Epileptic children had the highest, and the elderly had the lowest SMRs (97). In children, the SMR reached up to 22.25 (98) in the first year of life and 13.5 in the remaining groups of children.

2.2.6.1 Canadian studies for mortality in epilepsy

There are three Canadian studies of mortality in epilepsy. One is a population-based study for all causes of death in children with epilepsy and the two other studies measured epilepsy-related deaths, specifically SUDEP: one in children and one in adults.

The first study was conducted with the Nova Scotia childhood epilepsy cohort that included incident cases of epilepsy between 1977 and 1985 (99). Children aged from 28 days to 16 years were included. Children with neonatal seizures were excluded. The authors linked names and birth dates to the provincial death and marriage registries. The death certificates and autopsy reports were also reviewed for patients known to the authors.

Within the follow-up group of 686 PWE, 26 deaths were identified. Taking into account the reference population of Nova Scotia children and young people, children with epilepsy were 5.30 times more likely to die in 1980 and 8.80 more likely to die in 1999 than the general population (99).

The second study aimed to calculate the frequency and risk factors for SUDEP in Ontario's pediatric population (less than 18y). Cases of SUDEP were obtained from files of the Ontario Chief Coroner's Office, Ontario Pediatric Forensic Pathology Unit and anecdotal cases from the staff in the Division of Neurology at the Hospital for Sick Children in Toronto.

The authors identified 27 cases of SUDEP from 1988 to 1998 and calculated a crude rate of 2 per 10,000 person-years among children with epilepsy in Ontario in 1998 (16).

The last Canadian study investigated SUDEP in Saskatchewan among people aged 15 and 49 years. Cases of SUDEP were identified through hospital discharge codes and from the registry file linked to the Saskatchewan Health Database. Death certificates and available autopsy reports

were obtained for deaths outside of the hospital and deaths of unknown causes in PWE, death certificates and available autopsy reports were also obtained.

There were 39 cases of SUDEP between 1970 and 1990, giving a maximum overall incidence of SUDEP of 1.35 per 1,000 person-year (17).

Unfortunately, none of the studies measured all-cause mortality in PWE in all age group in Canada.

As individuals responsible for health policy development, implementation, and assessment uses this kind of information as a factual source for decision making (100) a study including age-specific mortality in epilepsy is of great importance.

Age and cause-specific mortality also provide an instant depiction of the health status of a population. Finally, information of temporal trends on mortality (by causes) substantiate the progress of health programs.

3.1.1 Study population

Saskatchewan is one of the prairie provinces of Canada covering 651,900 square kilometers (6.5% of Canada's 9,984,670 square kilometers). It shares a border with Alberta to the west, Manitoba to the east, Northwest Territories toward the north, and Montana and North Dakota (the USA) to the south (101).

Saskatchewan's populace (1,033,381 people in 2011) represents approximately 3% of the total population of Canada.

According to the 2011 census population of Saskatchewan, 50.5% of individuals were females and 49.5% were males. Children (under the age of 15) accounted for 19 % (197,855 individuals); the working age population (age 15 to 64 years) accounted for 66% (681,815 individuals); and seniors (aged 65 and over) accounted for 15% (153,705 individuals). This Saskatchewan age distribution is similar to the Canadian distribution by age group (16.7%, 68.5%, and 14.8% respectively) (102).

Also in 2011, Saskatchewan residents largely described themselves as being of European ancestry (76%)(103), self-identified Aboriginals (15.6%) (103), and others (8.4%).The largest component of self-identified Aboriginal residents were members of First Nations (66.6%) followed by Metis people (33.3%). This 16% of the self-identified Aboriginal proportion of Saskatchewan population represented the second highest proportion within all provinces in Canada, where the proportion of the population was 3.8% (104).

In Saskatchewan, all residents receiving medical coverage constituted the "covered population" for the present study, which did not include federally insured residents (such as federal prison inmates, individuals from the Canadian Forces and Royal Canadian Mounted Police).

Approval for this study was obtained from the Biomedical Research Ethics Board at the University of Saskatchewan (Bio# 15-225).

3.1.2 Data sources

The study was conducted using administrative data from the province of Saskatchewan and followed standards for epidemiologic studies and surveillance of epilepsy (94). The government of Saskatchewan maintains several databases of health services utilization for beneficiaries, which includes up to 99% of the provincial population. Data is linked at the patient-level through a unique personal Health Services Numbers for each individual (105).

The epilepsy database was created through linkage of the following health services claims data: Person Registry, Hospital Separation Data, and Physicians services data.

1. Person Registry: provides information on all residents eligible for Saskatchewan Health benefits and provides demographic information about the covered population.
2. Hospital Separation Data: this includes patient information on every discharge, transfer, or in-hospital death in Saskatchewan including diagnoses, procedures, and hospital admission/discharge dates. Records of inpatient separations and day surgeries for patients treated in hospitals are captured as well as out-of-province hospital separations for Saskatchewan health beneficiaries.
3. Physician's services data: this includes doctor and nurse practitioner service claims for payment from the provincial government for services provided to patients. Patient

information is included, as well as service information such as date, fee code, type, diagnosis code associated with service (maximum of one diagnosis code per service claim), location, and payment information (105). Physicians who are remunerated on a non-fee-for-service basis are also expected to submit same ‘shadow,' or ‘dummy’ billing claims to evaluate productivity.

The method of classification for diseases and related health problems in Saskatchewan hospitals before April 1, 2002, was based on the 9th revision of the International Classification of Diseases (ICD-9), allowing only 16 diagnoses per record (88). ICD-10-CA codes were introduced April 1, 2001, after which time approximately 30 % of hospitals in Saskatchewan continued to use ICD-9 codes. By April 1, 2002, the transition to ICD-10-CA codes was complete, and all hospitals were using this system to record up to 25 diagnoses per record (89).

The primary data files for this study were created and de-identified by epidemiologists at the Saskatchewan Ministry of Health (SMH) Public Health Branch (PHB) through a formal data sharing agreement between SMH and the University of Saskatchewan.

The data released contained a file with individual-level data from individuals with epilepsy (study identification, sex, year of birth, status at index (incidence or prevalent), index date, exit reason, and registered Indian status); and a file containing information allowing us to establish an appropriate denominator from the overall population (calendar date, sex, year of birth, registered Indian status, and frequency).

Registered Indians

Registered Indians (RI) were identified through a flag in the person registry from self-declaration to Saskatchewan Health. Information regarding the date of registration (initiation or withdrawal) was not reported.

Registered Indians or Status Indians are people who are registered with the federal government as Indians, which only include First Nation people. RI are entitled to some benefits that are not available to Non-Status Indians or Metis people such as on-reserve housing benefits, education, and exemption from federal, provincial and territorial taxes in specific situations (106)

Mortality

The date of death (month and year) was collected from the Person Health Registry System (PHRS) database. This registry requires a Medical Certificate of Death to be filled out by a medical examiner, physician or nurse practitioner. It also requires a Medical Statement of Death, which is filled out by a funeral director. It is also possible for the death to be reported directly to PHRS. This report needs to be accompanied by proof of the death (i.e., funeral director's Statement of Death).This would occur, for example, in the case of deaths which occur out of the country as the registry does not receive notifications for these deaths from any other agency.

Information on deaths gets uploaded to the PHRS database on a nightly basis. We did not receive information about the causes of death.

3.1.3 Cohort case definition algorithm

The cohort included individuals with at least two years of continuous provincial health coverage between January 1, 1999, and December 31, 2010, and also included children born between January 1, 1999, and December 31, 2010.

The specific criteria used to define cases of epilepsy were as follows:

1. During the period January 1, 2001, to December 31,2010 the subject had, at least, one hospital separation with a diagnosis of epilepsy (ICD-9 345 or ICD-10-Ca G40)

   or

2. During the period January 1, 1999, to December 31, 2010, the subject had at least two physician visits with a diagnosis of epilepsy (ICD-9 345 or ICD-10-Ca G40) on different dates within 730 days; the second of the two physician visits had to be on or after January 1, 2001. The medical services file was processed until the first pair of physician visit met these criteria. When this was met, the date of the first of the two physician visits was taken as the case date

This definition of epilepsy has been assessed in a previous Canadian study that included 2,253 charts. This study used as a gold standard chart review by two trained physicians in epilepsy management to determine if the patient had epilepsy, convulsions (but no epilepsy), or another condition. This was compared to the diagnosis based on cases of epilepsy identified by two physician billing claims or one hospital claim, resulting in a sensitivity of 89% (95% CI 85.4- 92.5) and specificity of 92.4% (95% CI 89.9- 94.9) (107) compared to the gold standard.

Population denominator

For the denominator, we used the supplied person registry to identify the covered population at the midpoint (July 1st) of each year. The denominator was stratified for various analyses by the calendar year (2005-2010), sex, year of birth, and RI status. Age was divided into eighteen groups (2-4, 5-9, 10-14,15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74-, 75-79, 80-84, 85-89 and >90). Note that information was lacking from the population under two years of age.

3.2 Analysis

3.2.1 Descriptive statistics

Incidence

Incident cases were defined as those patients newly diagnosed with epilepsy between January 1st, 2005 and Dec 31st, 2010. Data between January 1st, 2001 and Dec 31st, 2004 was used as a four-year washout period as per the standards for epidemiological studies and surveillance of epilepsy (94)

To measure the incidence rate (IR), we used the following formula (5):

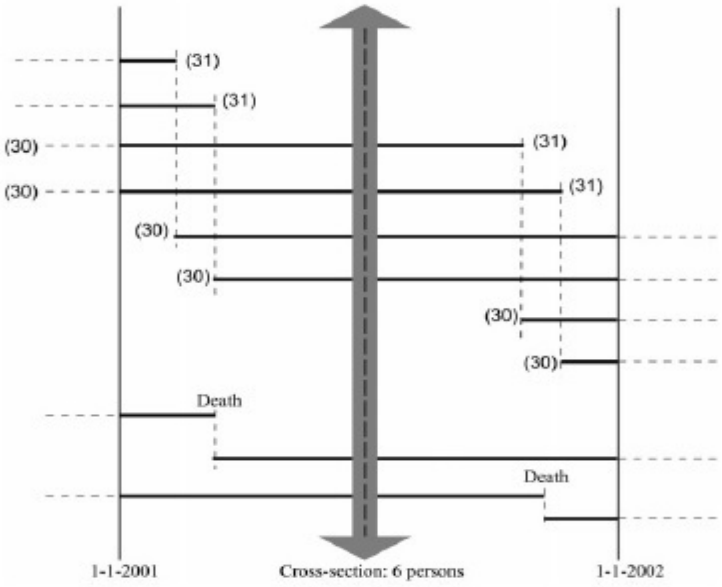
$$IR = \frac{Number\ of\ new\ cases\ of\ epilepsy\ during\ a\ given\ period}{total\ \text{person-time}\ of\ observation}$$

The numerator was the total number of new cases, which was divided by total person-time of observation to establish the incidence rate. Incidence was calculated for the entire observation period (2005 to 2010) and also calculated annually between 2005 and 2010.

To calculate the denominator, demographers generally calculate the average number of people in a given year by adding the number of people at the beginning and the end of the year and dividing this sum by two. That is the same as the expected number of people in the middle of the year, assuming a linear pattern of growth (108). The concept of incidence rate in a dynamic population was used by William Farr in the 1850s. He explained in detail the concept of the dynamic population as the basis for the calculation of the rate of morbidity(108). During each year in a dynamic population, some people leave the province or die while other people come to live in the province and babies are born. This means that individuals are not the same throughout the whole year, yet have to be, somewhat arbitrarily, defined by a particular "state," such as living in a particular province. The population of the province therefore also varies slightly from day to

day and would be artificially inflated if every person in the province at any time during the year were counted in the total. The “perfect” denominator would, of course, involve summation of all the individuals time period people were present in the province (commonly called person-years), but this would be unwieldy. Fortunately, using the mid-year population is a good approximation of this sum. For example, as long as the rate of people coming and going during the year is roughly similar, considering one person present for four months and another present for 8 months as equivalent to one person present for the whole years is a reasonable approximation. Calculation of incidence rate base in a dynamic population is then fairly straightforward. Thus, the denominator (total ”person-time” of observation) in this study, was the covered Saskatchewan population as for July 01 for each year, excluding prevalent cases.

Figure 3.1 Expected number of people in a dynamic population(108)



Small scale example, a dynamic population of 30-year-olds that is in steady state during the year 2001. The trajectory of individuals over time is indicated by bold lines. There are two types of 30-year-olds in the course of the year: those who were already 30 years old on 1 January and those who will become 30 years old during the year. The steady state assumes that each time a 30-year-old becomes a 31-year-old, (s)he is replaced by a 29-year-old who becomes a 30-year-old (four new persons in the figure). It also assumes that when a 30-year-old dies (the two bottom lines in the figure), they are replaced by a 29-year-old who becomes a 30-year-old on that day. Thus, on each day there are six individuals who are aged 30 years. On subsequent days, the individuals are different (in total 12 persons contribute to 6 person-years of 30-year-olds). The cross-section in the middle of the year represents the 'average' number of individuals alive during the year. We can calculate the number of person-years in two ways: either by adding all person–time for 30-year-olds or, much simpler, by assessing how many 30-year-olds are present on any day and multiplying this by the time window of 1 year. The incidence rate of death is calculated as two deaths divided by 6 persons-years, conventionally expressed as 33 per 100 person-years (figure adapted from Vandenbroucke *et al.*)[15]

The 95%CI was calculated with the following formula(109):

95%CI=$IR \pm 1.96\sqrt{\bar{x}/T^2}$

IR is stated as a decimal fraction (e.g., 0.10 per person-years not 10 per 100 person-years)

x is the number of new cases

T is the total number of person-time units observed

The age-standardized incidence was calculated by the direct method using the 2006 Canadian population as the standard population. Adjustment is accomplished by first multiplying

the age-specific rates of disease by age-specific weights. The weights used in the age-adjustment of epilepsy data were the proportion of the 2006 Canadian population within each age group. The weighted rates are then summed across the age groups to give the age-standardized rate and was reported per 100,000. We followed the formula (110):

$$\text{Age-standardized rate} = \frac{Total\ expected\ cases}{General\ population\ rate} \times 100{,}000$$

The 95% confidence interval for age-standardized rates were calculated based on a standard error following the formula:

$$SE = R/\sqrt{N}$$

where:

R = (age-standardized) total rate

N = number of events

The estimated SE was then used to compute a 95% confidence interval (CI) for the rate.

The standard formula for determining the 95% CI of a rate was(111):

$$95\%CI = R \pm (1.96 \times SE)$$

Prevalence

The prevalence (P) was calculated using the following formula (5):

$$P = \frac{Number\ of\ existing\ cases\ of\ epilepsy\ during\ a\ specified\ period}{Average\ population\ during\ that\ time\ period} \times 1{,}000$$

The numerator was the number of existing alive cases of epilepsy each year for 2005 to 2010. The denominator was the average covered population on July 01 of each specific year.

The 95% confidence intervals for prevalence was calculated using the score method with the following formula (109):

95%CI= $p \pm 1.96\ (\sqrt{p\ (1-p))/(n+4)})$

where p = (x + 2)/(n + 4)

p refers to the standardized sample proportion (prevalence stated as a decimal fraction)

n is the appropriate denominator

x is the appropriate numerator

The prevalence was age-standardized by the direct method using the 2006 total Canadian population as standard population using the above formula(110).

The 95% confidence interval for age-standardized prevalence was calculated based on a standard error (111).

Mortality

The Standardized Mortality Ratio (SMR) was calculated with indirect standardization formula(110):

$$SMR = \frac{Observed\ number\ of\ deaths}{Expected\ number\ of\ deaths}$$

The all-cause mortality of patients with epilepsy was calculated for the six-year interval 2005 to 2010, and for each calendar year. The unit of study was person-years. For each age group, we computed mortality rates for persons in the general population (Saskatchewan Population) based on specific mortality data of the province from Statistics Canada. These rates were then

applied to the age- and sex-specific exposure times for persons in the study with a diagnosis of epilepsy. This yielded an expected number of deaths. The ratio of observed to expected number of deaths was the standardized mortality ratio (SMR).

The 95% confidence interval (95% CI) of the SMR was calculated, assuming a Poisson distribution for the observed number of deaths following the formula (112):

Lower: $\frac{O}{E}\left(1-\frac{1}{9\ x\ O}-\frac{1.96}{3\sqrt{O}}\right)^3$

Upper: $\frac{O+1}{E}\left(1-\frac{1}{9\,(\,O+1}+\frac{1.96}{3\sqrt{O}+1}\right)^3$

O refers to the observed mortality rate

E refers to the expected mortality rate

A *p*-value of <0.05 was considered to be statistically significant for all the analysis.

3.2.2 Statistical Inference

For incidence and prevalence, we calculated the changes between 2005 and 2010 in absolute numbers. For a measure of association between incidence rate of epilepsy for sex, and RI status we calculated the rate ratio (RR). The rate ratio (RR) was calculated to measure contributions to the incidence of epilepsy due to demographic characteristics (male, and RI status, and the difference in time) using the following formula (113):

$$RR = IR\ (with\ demographic\ characteristics / IR\ (non-demographic\ characteristics$$

We explored significant changes ($p < 0.05$) using X^2 test, and 95% confidence intervals (95%CI).

The prevalence ratio (PR) was used for measures of association between two prevalences, calculated with the following formula (114):

$PR = \text{prevalence}_D / \text{prevalence}_O$

where $\text{prevalence}_{(D)} = a/(a+b)$ (a= cases of the disease with the demographic characteristic and b= cases free of disease with the demographic characteristics

$\text{prevalence}_O = c/(c+d)$ (c=cases of the disease without the demographic characteristic and d=cases free of disease without the demographic characteristic)

We tested for significant changes ($p < 0.05$) using X^2 test and 95% confidence intervals (95%CI)(113).

CHAPTER 4: RESULTS

4.1 Incidence of epilepsy in Saskatchewan

4.1.1 Overall incidence of epilepsy in general population

Analysis of our Ministry of Health (Saskatchewan, Canada) data files revealed a total of 6,060,356 person-years of follow-up in Saskatchewan, Canada, for the development of epilepsy between 2005 and 2010. A total of 3,804 new epilepsy patients were found, giving a crude overall incidence rate of 62.8 per 100,000 person-years (95%CI = 60.8, 64.8) and the age-standardized (for the 2006 Canadian population) incidence of 61.98 per 100,000 person-years (95% CI= 60.0, 63.9). The cases included 2025 (53.2%) male patients and 1779 (46.8%) female patients. Age-standardized incidences were 66.8 (95%CI: 63.9, 69.7) for male patients and 57.1 (95%CI: 54.5, 59.8) for female patients (Table 4.1).

4.1.2 Age-specific incidence of epilepsy in the general population

Using cumulative data from 2005-2010, we found fluctuations in epilepsy incidences within the younger age groups but an increasing incidence toward a high point in the75-79 age group (133.5/100,000 person-years) (Table 4.2). The age-specific incidence was similar in males and females in the 5-39 year group. In individuals older than 39 years, the incidence in men was consistently higher than women (Figure 4.1).

4.1.3 Temporal changes of incidence in the general population

As shown in Figure 4.2, there was a decreasing trend over time in the age-standardized incidence of epilepsy. From 2005 to 2010, the annual incidence of epilepsy decreased from 69.5/100,000 in 2005 to 43.9/100,000 in 2010 (RR = 0.63; 95% CI 0.56–0.71, $p < 0.0001$) (Table 4.3).

A significant decrease in incidence between beginning and the end of the study period occurred in both men (from 72.4/100,000 to 48.6/100,000; RR: 0.67; 0.57–0.78, p = <0.0001) and women (from 66.5/100,000 to 39.2/100,000; RR: 0.59; 0.49–0.70, p = <0.0001) (Table 4.3 and Figure 4.2)

4.1.4 Incidence of epilepsy in self-declared Registered Indians (RI)

In the RI group there were 608 patients with a diagnosis of new-onset epilepsy over the cumulative period 2005-2010 with 639,972 person-years of follow-up, resulting in a crude incidence of epilepsy in this group of 95 per 100,000 person-years (95%CI: 87.4, 102.6) and age-standardized incidence of 121.9 per 100,000 person-years (95%CI: 112.2, 131.6). The age-standardized incidence in males was 140.4 per 100,000 person-years (95%CI: 125.2, 154.5) and the incidence in females was 104.7 (95%CI: 92.4, 116.7).

4.1.4.1 Differences in the incidence of epilepsy between Registered Indians vs. not Registered Indians

The age-standardized incidence of epilepsy for RI compared with non-RI is shown in Table 4.4. This shows an overall (male and females together) rate ratio of 1.62 (95% CI: 1.49, 1.77) for the incidence of epilepsy among RI compared with non-RI. In other words, people who ever self-identified as RI were approximately 1.62 times more likely (*p*=<0.001) to be newly diagnosed with epilepsy than people who never self-identified as RI in Saskatchewan. These differences were statistically significant in both sexes. RI males were 1.66 (95% CI 1.47, 1.86) more likely to be newly diagnosed with epilepsy than non-RI males.

Similarly, RI females were 1.58 times (95% CI= 1.39, 1.80) more likely to be newly-diagnosed with epilepsy than non- RI females.

The age-specific distribution of epilepsy among RI compared to non-RI in Saskatchewan between 2005 and 2010 showed that from the 15-19 age group to the 65-69 age group, the incidence of epilepsy was significantly higher (p=<0.05) among RI compared to non-RI, with the highest rate ratio of 4.52 (95%CI= 3.39, 6.05) in the 45-49 age group (Table 4.5 Comparison of age-specific incidence of epilepsy per 100,000 person-years between Registered Indians vs. non-Registered Indians for the period of 2005-2010 and Figure 4.3).

4.1.4.2 Age-specific incidence of epilepsy in self-declared Registered Indians

Over the cumulative period of 2005-2010, the incidence of epilepsy in RI varied by age group (Table 4.6 and Figure 4.3). The highest incidence was the 55-59 age group at 216.4 per 100,000 person-years (95%CI: 146.7, 286.2) and lowest (zero incidences) in the 80-84 group age.

Table 4.1 Crude and age-standardized incidence of epilepsy in Saskatchewan, Canada by year and sex for the period 2005-2010

	2005	2006	2007	2008	2009	2010	2005-2010
Person per years population							
Males	497111	489006	494314	505500	507392	520422	3127425
Females	503413	497018	500735	509700	512668	523077	3143868
Overall	1000524	986024	995049	1015200	1020060	1043499	6271293
Incidence cases							
Males	360	429	344	351	291	253	2025
Females	335	357	283	305	308	205	1779
Overall	695	786	627	656	599	458	3804
Crude incidence per 100,000 (95%CI)							
Male	72.4 (64.9,79.9)	87.7 (79.4, 96.0)	69.6(62.2, 76.7)	69.4(62.5, 77.2)	57.35 (50.8, 63.9)	48.6(42.6, 54.6)	67.19(64.3,70.1)
Female	66.5 (59.4, 73.7)	71.8(64.4, 79.3)	56.5(53.1, 66.5)	59.8(52.1, 67.7)	60.08(53.4, 66.8)	39.2 (33.8, 44.6)	58.39(55.7,61.1)
Overall	69.5 (64.3, 74.6)	79.7(74.1, 85.3)	64.0(59.7, 69.6)	64.6 (60.6, 70.8)	58.72(54.0, 63.4)	43.9(39.9, 47.9)	62.77(60.8,64.8)
Age-standardized incidence per 100,000[2] (95%CI) [2]							
Male	72.0(64.6, 79.5)	86.9 (75.7,91.6)	69.1(61.9, 76.4)	69.9(62.6, 77.2)	56.8(50.2, 63.3)	48.0(42.1, 54)	66.8(63.9,69.7)
Female	64.8(57.9, 71.8)	69.9 (61.2, 75.3)	58.4(51.9, 65)	58.9(52.3, 65.5)	58.8(52.2,65.3)	38.4(33.2, 43.7)	57.1(54.46,59.8)
Overall	68.1(63.3, 73.5)	78.4 (72.5, 83.4)	63.8(58.9, 68.7)	65.7(60.7, 70.7)	57.8(53.1, 62.4)	43.3(39.3, 47.5)	62(60,63.9)

2 Standardized for the 2006 Canadian Population

Table 4.2 Age-specific incidence of epilepsy per 100,000 person-years in Saskatchewan, Canada, for the cumulative period of 2005-2010

	Age group (years)	New cases	Average Population	Crude prevalence Per 1,000	95% CI	
					Lower	Upper
Overall						
	2-4	119	228213	52.1	42.8	61.5
	5 to 9	185	377709	49.0	41.9	56.0
	10 to 14	169	410366	41.2	35.0	47.4
	15-19	286	461158	62.0	55.0	69.2
	20-24	224	465705	48.1	41.8	54.4
	25-29	185	425800	43.4	37.2	49.7
	30-34	182	386438	47.1	40.2	53.9
	35-39	216	374422	57.7	50.0	65.4
	40-44	204	414987	49.2	42.4	55.9
	45-49	283	471302	60.0	53.0	67.0
	50-54	299	451319	66.2	58.7	73.8
	55-59	263	377696	69.6	61.2	78.0
	60-64	218	297866	73.2	63.5	82.9
	65-69	203	232099	87.5	75.4	99.5
	70-74	211	200895	105.0	90.9	119.2
	75-79	220	180566	121.8	105.7	137.9
	80-84	180	171492	105	89.6	120.3
	85-89	157	132323	118.6	100.1	137.2
	Total	3804	6060356	62.8	60.8	64.8

95%CI= 95% confidence intervals

Figure 4.1 Age-specific incidence of epilepsy by gender in Saskatchewan, Canada, 2005-2010

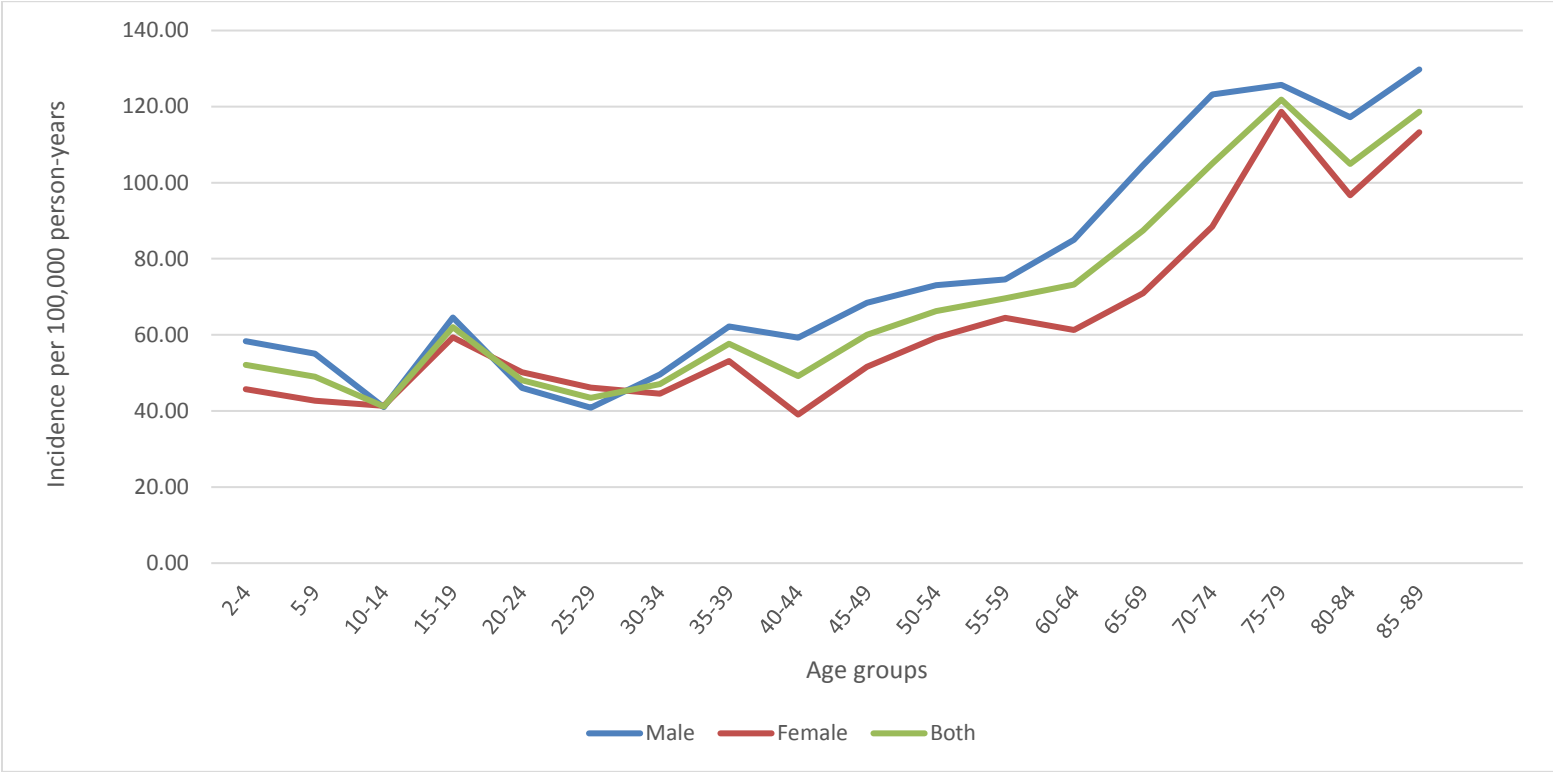
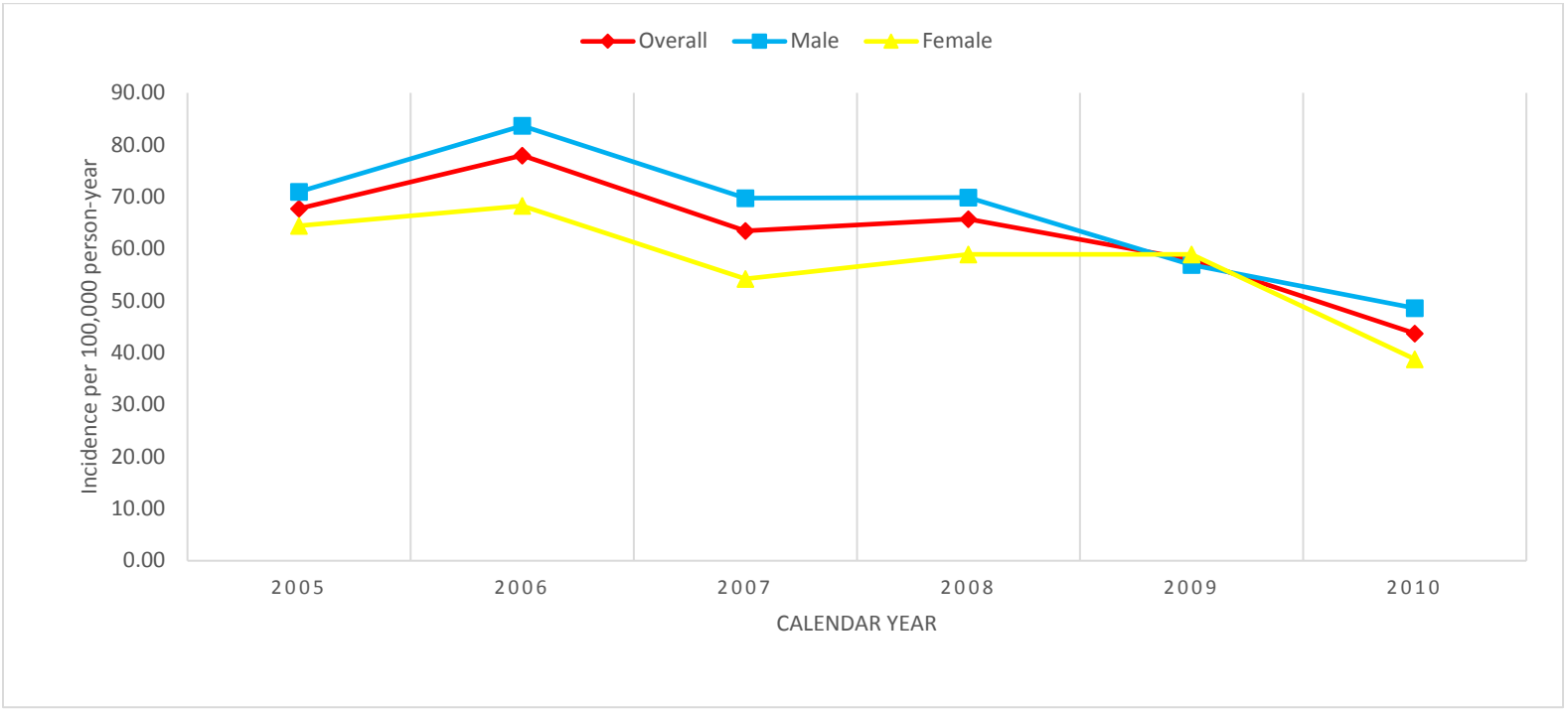


Figure 4.2 Age-standardized incidence of epilepsy in Saskatchewan, Canada, 2005-2010



Age-standardized to the 2006 Canadian census population

Table 4.3 Changes in the incidence of epilepsy by sex in Saskatchewan, Canada, between 2005 and 2010

	2005				2010				Changes between 2005 and 2010				
	n	%	Crude rate per 100,000 person-years(CI)	Age-standardized rate per 100,000 person-years(CI)	n	%	Crude rate per 100,000 person-year(CI)	Age-standardized rate per 100,000 person-years(CI)	n	% change	Rate ratio	CI	*p*
Male	360	51.8	72.4 (64.9,79.9)	72(64.6, 79.5)	253	55.24	48.6(42.6, 54.6)	48.0(42.1, 54)	107	-30.5	0.67	0.57, 0.78	<0.001
Female	335	48.2	66.5 (59.4, 73.7)	64.8(57.9, 71.8)	205	44.76	39.2 (33.8,44.6)	38.4(33.2, 43.7)	130	-40.5	0.59	0.49, 0.70	<0.001
Overall	695	-	69.5 (64.3, 74.6)	68.4(63.3, 73.5)	458	-	43.9(39.9, 47.9)	43.3(39.3, 47.2)	237	-34.7	0.63	0.56,0.71	<0.001

2 Standardized for the 2006 Canadian Population

95% CI=Confidence interval; RR= rate ratio; p significant= < 0.05

Table 4.4 Comparison of age-standardized incidence of epilepsy per 100,000 person-years between Registered Indians vs. non-Registered Indians for the cumulative period of 2005-2010

	Ever self-identified RI		Never self-Identified RI				
	Age-standardized incidence per 100,000 person-years	95% CI	Age-standardized incidence per 100,000 person-years	95%CI	Rate ratio	95% CI	*p*
Male	140.4	125.2, 154.5	51.4	48.7, 54.0	1.66	1.47,1.86	<0.001
Female	104.7	92.5, 116.7	46.2	43.7, 48.7	1.58	1.39, 1.80	<0.001
Overall	121.9	112.2, 131.6	48.8	47.0, 50.6	1.62	1.49,1.77	<0.001

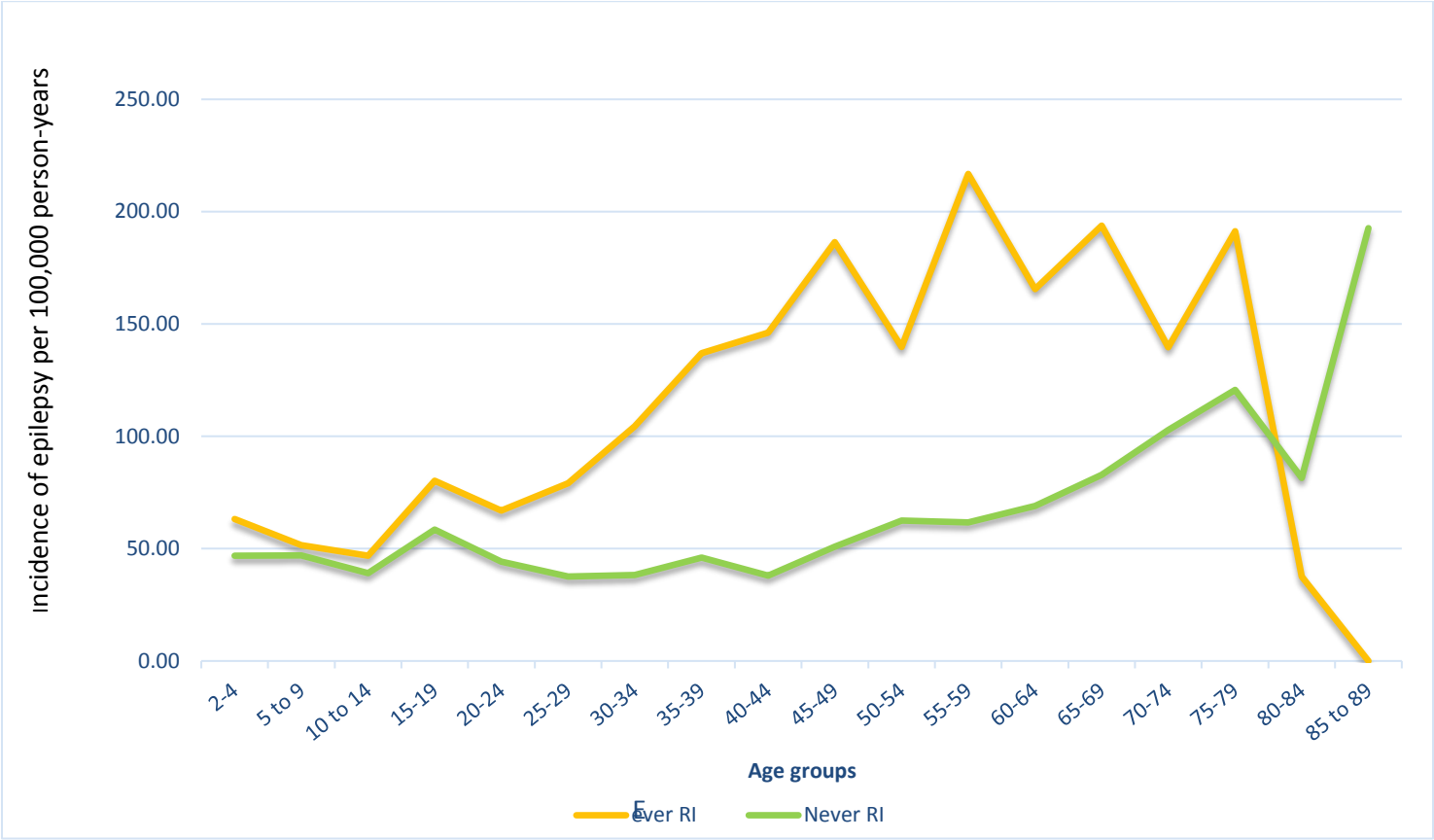
Age-standardized to the 2006 Canadian census population, 95%CI= confidence intervals; significant p= <0.05

Table 4.5 Comparison of age-specific incidence of epilepsy per 100,000 person-years between Registered Indians vs. non-Registered Indians for the period of 2005-2010

Age group	Ever self-identified RI				Never self-identified as RI				Rate ratio	95% CI	*p*
	New cases	Person per-years population	Crude rate	95% CI	New cases	Person per-year population	Crude rate	95% CI			
2-4	34	53164	63.9	42.5, 85.4	80	175049	45.7	35.7, 55.7	1.49	0.93, 2.08	0.10
5-9	42	81705	51.4	35.9, 66.9	116	296004	39.2	32.1, 46.3	1.31	0.92, 1.86	0.14
10-14	37	77683	47.6	32.3, 63.0	119	332683	35.8	29.3, 42.2	1.33	0.92, 1.92	0.13
15-19	61	76868	79.4	59.4, 99.3	196	384290	51.0	43.9, 58.1	1.55	1.17,2.07	0.003
20-24	43	63760	67.4	47.3, 87.6	153	401945	38.1	32.0, 44.1	1.77	1.26,2.48	0.001
25-29	41	51078	80.3	55.7, 104.8	121	374722	32.3	26.5, 38.0	2.48	1.74,3.54	<0.001
30-34	48	45378	105.8	75.8, 135.7	105	341060	30.8	24.9, 36.7	3.43	2.44,4.83	<0.001
35-39	60	43915	136.6	102.1, 171.2	144	330507	43.6	36.4, 50.7	3.13	2.32, 4.24	<0.001
40-44	58	39651	146.3	108.6, 183.9	123	375336	32.8	27.0, 38.6	4.46	3.27, 6.10	<0.001
45-49	61	32682	186.6	139.8, 233.5	181	438620	41.3	35.2, 47.3	4.52	3.39,6.05	<0.001
50-54	34	24182	140.6	93.3, 187.9	231	427137	54.1	47.1, 61.1	2.60	1.81, 3.72	<0.001
55-59	37	17096	216.4	146.7, 286.2	191	360600	53.0	45.5, 60.5	4.08	2.87, 5.81	<0.001
60-64	20	11902	168.0	94.4, 241.7	177	285964	61.9	52.8, 71.0	2.71	1.71, 4.31	<0.001
65-69	16	8135	196.7	100.3, 293.0	152	223964	67.9	57.1, 78.7	2.89	1.73,4.85	<0.001
70-74	8	5620	142.3	43.7, 241.0	197	195275	100.9	86.8, 115.0	1.41	0.69, 2.86	0.33
75-79	7	3712	188.6	48.9, 328.3	171	176854	96.7	82.2, 111.2	1.95	0.92, 4.15	0.11
80-84	1	2199	45.5	-43.7, 134.6	153	169293	90.4	76.1, 104.7	0.50	0.07, 3.59	0.55
85-89	0	1242	0.00	0.00	134	131049	102.2	84.9, 119.6	0.00	0.00, 2.38	0.28
Total	608	639972	95.0	87.4, 102.6	2744	5420352	50.6	48.7, 52.5	1.87	1.72, 2.05	<0.001

95% CI= 95% Confidence interval; RR= rate ratio; p significant= < 0.05

Figure 4.3 Age-specific incidence of epilepsy by Registered Indian status in Saskatchewan, Canada, 2005-2010



4.2 Prevalence of epilepsy in Saskatchewan

4.2.1 Overall prevalence in the general population

The total number of people in Saskatchewan, Canada, living with epilepsy in 2010 was 8,880, representing a crude prevalence of 8.5 per 1,000 people (95%CI=8.3, 8.7). After adjustment to the Canadian population in 2006, the prevalence of epilepsy in Saskatchewan was 8.8 per 1,000 people (95%CI= 8.6, 9.0). The prevalent cases included 4,635 (52.2%) males and 4,245 (47.8%) females, resulting in age-standardized prevalence of 9.2 per 1,000 people (95%CI=8.9, 9.4) in males and 8.4 per 1,000 people (95%CI=8.5, 8.7) in females. (Table 4.6)

4.2.2 Age-specific prevalence in the general population

Table 4.7 and Figure 4.4 show the age-specific prevalence of epilepsy in Saskatchewan for 2010. There was a trimodal pattern in the overall age-specific epilepsy prevalence with peaks in the 15-19 age group (8.7 per 1,000 people; 95% CI 8.0, 9.4), the 35-39 age group (12.5 per 1,000 people; 95%CI=11.6, 13.4) and then a slow rise towards the 80-84 age group (11.9 per 1,000 people; 95%CI= 10.6, 13.3).

4.2.3 Temporal trends in the prevalence of epilepsy in the general population

Over the six-year study period (2005-2010), the overall midyear population decreased from 1,046,964 to 1,043,467 (Figure 4.5). However, the absolute number of overall prevalent cases of epilepsy increased each year from 6,637in 2005 to 8,800 in 2010 (see Table 4.6) resulting in a significant increase (p=<0.001) in the age-standardized prevalence from 6.6 in 2005 (95%CI=6.2, 6.5) to 8.8 per 1,000 people in 2010 (95%CI=8.6, 9.0) (Table 4.8).

Table 4.6 Annual prevalence of epilepsy per 1,000 people in Saskatchewan

	2005	2006	2007	2008	2009	2010
Midyear population						
Males	522085	489006	494314	505500	507392	520390
Females	524879	497018	500735	509700	512668	523077
Overall	1046964	986024	995049	1015200	1020060	1043467
Prevalence cases						
Males	3463	3704	4016	4242	4474	4635
Females	3174	3422	3673	3860	4058	4245
Overall	6637	7126	7689	8102	8532	8880
Crude prevalence per 1,000 people (95%CI)						
Male	6.6(6.4, 6.8)	7.6(7.3, 7.8)	8.0(7.7, 8.2)	8.4(8.1, 8.6)	8.7(8.5, 9.0)	8.9 (8.7, 9.2)
Female	6.0 (5.8, 6.3)	6.9(6.7, 7.1)	7.2(6.9, 7.4)	7.5(7.3, 7.8)	7.9(7.6, 8.1)	8.1(7.9, 8.4)
Overall	6.3(6.2, 6.5)	7.2(7.1, 7.4)	7.7(7.6, 7.9)	8.0(7.8, 8.2)	8.4(8.2, 8.5)	8.5(8.3, 8.7)
% of change between each year	14%	6.9%	3.2%	4.7%	0.7%	
Age-standardized prevalence per 1,000 (95%CI)[2]						
Male	6.8 (6.6, 7.1)	7.7 (7.5, 8.0)	8.3(8.0, 8.6)	8.6(8.3, 8.8)	9.0(8.8, 9.3)	9.2(8.9, 9.4)
Female	6.3 (6.1, 6.5)	7.1 (6.9, 7.4)	7.6(7.3, 7.8)	7.8(7.6, 8.1)	8.2(7.9, 8.4)	8.4(8.1, 8.7)
Overall	6.6 (6.4, 6.7)	7.4(7.3, 7.6)	7.9(7.8, 8.1)	8.2(8.0, 8.4)	8.6(8.4, 8.8)	8.8(8.6, 9.0)

2 Standardized for the 2006 Canadian Population

Figure 4.4 Age-specific prevalence of epilepsy in Saskatchewan, 2010

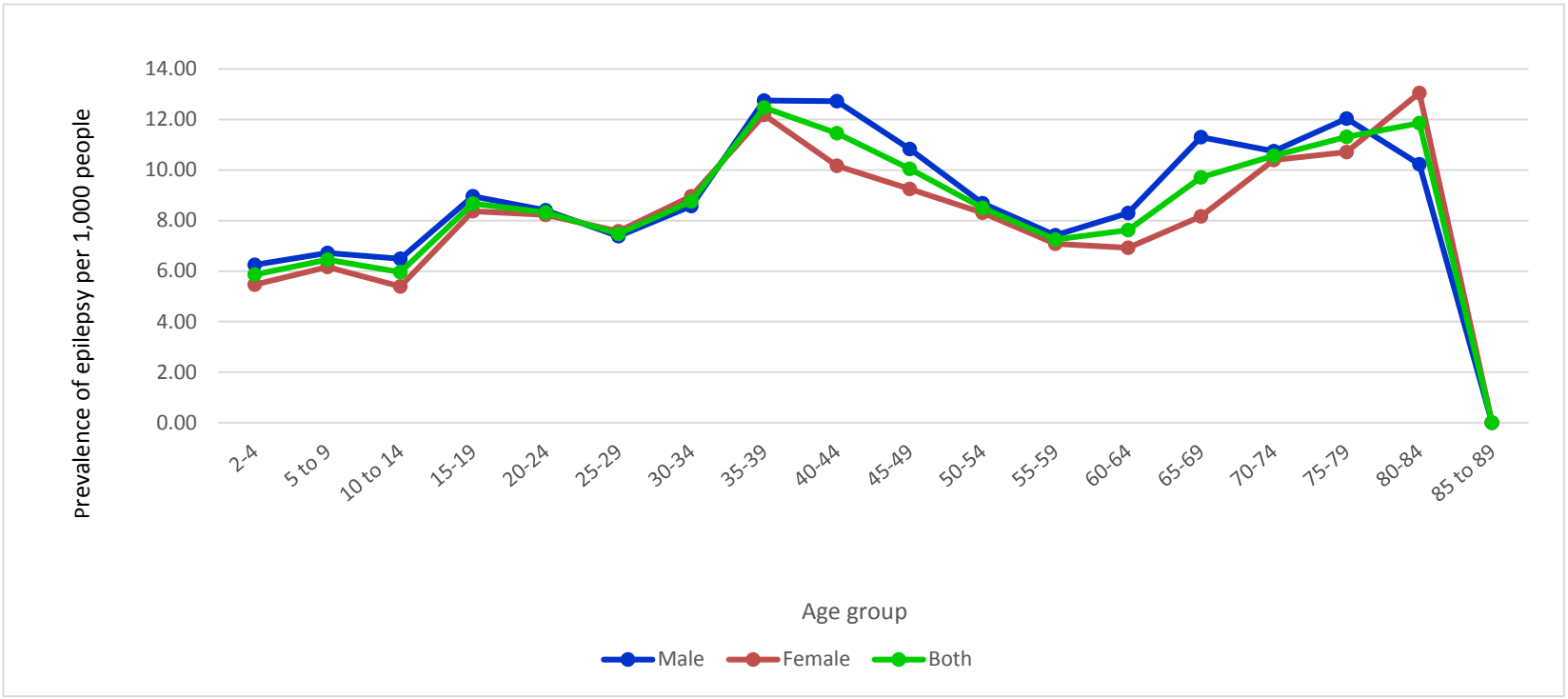


Table 4.7 Age-specific prevalence of epilepsy per 1,000 people in Saskatchewan, Canada, for 2010

	Age group (years)	Identified cases	Midyear population	Crude prevalence Per 1,000 people	95% CI	
					Lower	Upper
Overall						
	2-4	246	41936	5.9	5.2	6.6
	5 to 9	417	64674	6.4	5.9	7.1
	10 to 14	397	66674	5.9	5.4	6.6
	15-19	646	74462	8.7	8.0	9.4
	20-24	662	79569	8.3	7.7	9.0
	25-29	576	77070	7.5	6.9	8.1
	30-34	615	70184	8.8	8.1	9.5
	35-39	813	65185	12.5	11.6	13.4
	40-44	742	64754	11.5	10.7	12.3
	45-49	783	77968	10.0	9.4	10.8
	50-54	669	78658	8.5	7.9	9.2
	55-59	507	69908	7.2	6.6	7.9
	60-64	430	56448	7.6	6.9	8.4
	65-69	398	40970	9.7	8.8	10.7
	70-74	357	33788	10.6	9.5	11.7
	75-79	332	29338	11.3	10.2	12.6
	80-84	290	24459	11.9	10.6	13.3
	85-89	0	27422	0.00	0	0
	Total	8880	1043467	8.5	8.3	8.7

CI= 95% confidence intervals

Figure 4.5 Annual age-standardized prevalence of epilepsy in Saskatchewan, Canada, 2005-2010

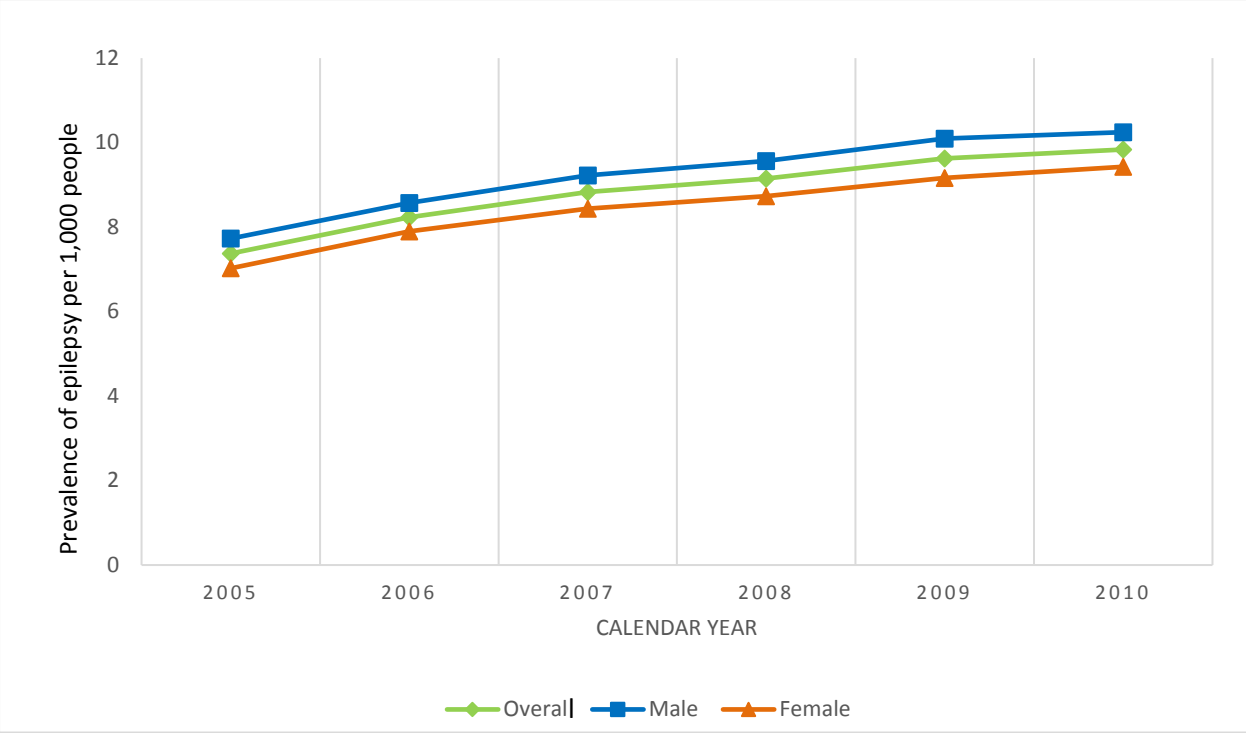


Table 4.8 Changes in the prevalence of epilepsy in Saskatchewan, Canada, between 2005 and 2010

	2005				2010				Changes between 2005 and 2010				
	Existent cases	%	Crude rate per 1,000 People(CI)	Age-adjusted rate per 1,000 people(CI)	Existent cases	%	Crude rate per 1,000 people(CI)	Age-adjusted rate per 1,000 people(CI)	n	%	PR	95%CI	*p*
Male	3463	52.2	6.6(6.4, 6.9)	6.8 (6.6, 7.1)	4635	52.2	8.9(8.7, 9.2)	9.2(8.9, 9.4)	1172	0	1.34	1.28, 1.40	<0.001
Female	3174	47.8	6.0(5.8, 6.3)	6.3 (6.1, 6.5)	4245	47.8	8.1(7.9, 8.4)	8.4(8.1, 8.7)	1071	0	1.34	1.28, 1.40	<0.001
Overall	6637	-----	6.3(6.2, 6.5)	6.6 (6.4, 6.7)	8880	----	8.5(8.3, 8.7)	8.8(8.6, 9.0)	2243		1.34	1.30, 1.38	<0.001

n= number of existent cases, %= percentage, CI= 95% confidence intervals; *p*= <0.05; PR= prevalence ratio

Age-adjusted to the 2006 Canadian population.

4.3 Mortality of epilepsy in Saskatchewan

4.3.1 Overall all-cause mortality

SMRs and specific death rates for epilepsy were calculated cumulatively (period 2005-2010) as well as annually. A total of 1470 deaths (816 in males and 654 in females) occurred during 6,307,668 person-years follow-up period (2005-2010) in patients with epilepsy. During the same period, 76,122 people died from all causes in the general population of Saskatchewan resulting in an expected number of 599.94 deaths (expected number = mortality rate in the general population of Saskatchewan times number of people with epilepsy). The overall all-cause SMR for epilepsy based on the study group was therefore 2.45 (95%CI 2.33, 2.58) (observed number of deaths/ expected number of deaths: 1470/599.94) (Table 4.9).

By sex, the SMR was 2.66 (95%CI 2.48, 2.85) for male, and 2.24 (95%CI 2.07, 2.42) for females.

4.3.2 Age-specific all causes of mortality

Analysis of age-specific mortality rates (Table 4.9) revealed significantly higher SMR in people with epilepsy in all age groups. The highest overall SMR was observed in children in the 5-9 age groups (SMR 19.68; 95% CI=6.25, 30.27) and the 10-14 years age groups (SMR 22.6; 95% CI=8.75, 40.07). The lowest SMR was found in 2-4 years group (SMR: 1.40: 95%CI 0.10, 3.37) and the 75-79 age group (SMR 1.89; 95% CI= 1.64, 2.14) (see Figure 4.6)

4.3.3 SMR temporal trends for all causes of mortality

Over the six-year period of the study, the SMR for both sexes together remained fairly constant, but sex-specific rates showed some fluctuation over the years, as shown in Figure 4.7.

Table 4.9 Cumulative age-specific distribution of Standardized Mortality ratios of all-cause mortality among patients with epilepsy vs. the general population in Saskatchewan, Canada, for the period 2005-2010

	No. of deaths												
	Male					Female				Overall			
	Obs	Exp	SMR	95% CI Lower	Upper	Obs	Exp	SMR	95%CI lower upper	Obs	Exp	SMR	95%CI lower	Upper
Overall	816	307.14	2.66	2.48, 2.85		654	292.30	2.24	2.07, 2.42	1470	599.94	2.45	2.33	2.58
Age group(y)														
2-4	1	1.21	0.83	0.01, 4.59		1	0.94	1.07	0.01, 5.94	2	2.14	1.40	0.10	3.37
5 to 9	3	0.19	15.75	3.17, 46.02		3	0.16	18.72	3.76, 54.68	6	0.35	19.68	6.25	37.27
10 to 14	5	0.21	23.34	7.52, 54.48		3	0.18	16.80	3.38, 49.10	8	0.39	22.60	8.75	40.07
15-19	4	1.97	2.03	0.55, 5.19		3	0.86	3.50	0.70, 10.22	7	2.79	2.84	1.00	5.16
20-24	5	2.19	2.28	0.73, 5.32		8	1.02	7.82	3.37, 15.40	13	3.20	4.35	2.16	6.95
25-29	14	1.69	8.29	4.53, 13.91		4	0.78	5.11	1.37, 13.07	18	2.46	7.67	4.33	11.54
30-34	15	1.90	7.88	4.41, 13.01		9	1.17	7.67	3.50, 14.57	24	3.09	8.05	4.97	11.54
35-39	23	3.45	6.66	4.22, 10.00		18	1.90	9.49	5.62, 15.00	41	5.33	7.86	5.52	10.44
40-44	33	5.87	5.62	3.87, 7.89		21	2.81	7.46	4.62, 11.41	54	8.47	6.48	4.79	8.32
45-49	44	7.53	5.84	4.25, 7.84		26	3.87	6.72	4.39, 9.85	70	11.16	6.35	4.89	7.92
50-54	64	8.58	7.46	5.75, 9.53		43	5.20	8.27	5.98, 11.14	107	13.68	7.89	6.41	9.45
55-59	72	9.06	7.95	6.22, 10.01		41	5.45	7.52	5.40, 10.20	113	14.42	7.90	6.46	9.42
60-64	56	13.24	4.23	3.19, 5.49		36	6.28	5.73	4.02, 7.94	92	19.06	4.87	3.89	5.92
65-69	59	21.45	2.75	2.09, 3.55		43	10.77	3.99	2.89, 5.38	102	31.33	3.28	2.65	3.95
70-74	88	28.59	3.08	2.47, 3.79		41	18.50	2.22	1.59, 3.01	129	46.75	2.78	2.30	3.28
75-79	79	45.14	1.75	1.39, 2.18		83	29.80	2.78	2.22, 3.45	162	73.93	2.20	1.87	2.56
80-84	115	58.99	1.95	1.61, 2.34		106	57.67	1.84	1.50, 2.22	221	117.68	1.89	1.64	2.14
85 to 89	136	0.00	0.00			165	0.00	0.00		301	0.00	0.00		

95%CI = 95% confidence interval; Exp = expected; Obs = observed; SMR = standardized mortality ratio

Figure 4.6 Age-specific Standardized Mortality Ratio for epilepsy in Saskatchewan, Canada, 2005-2010

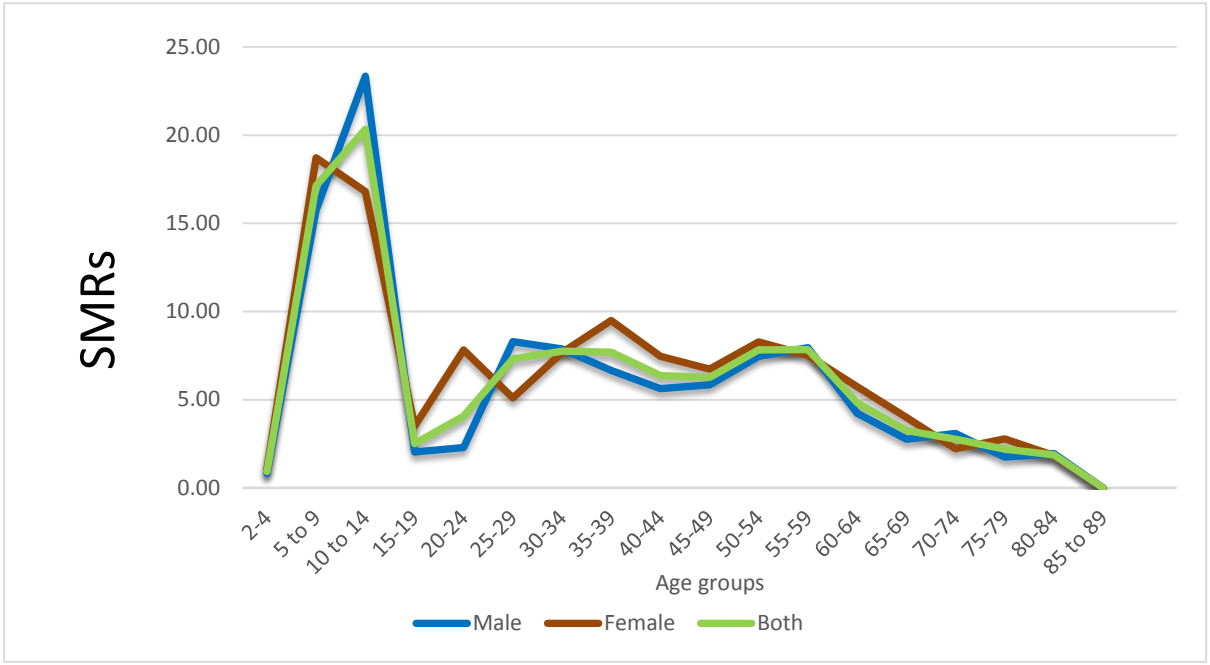
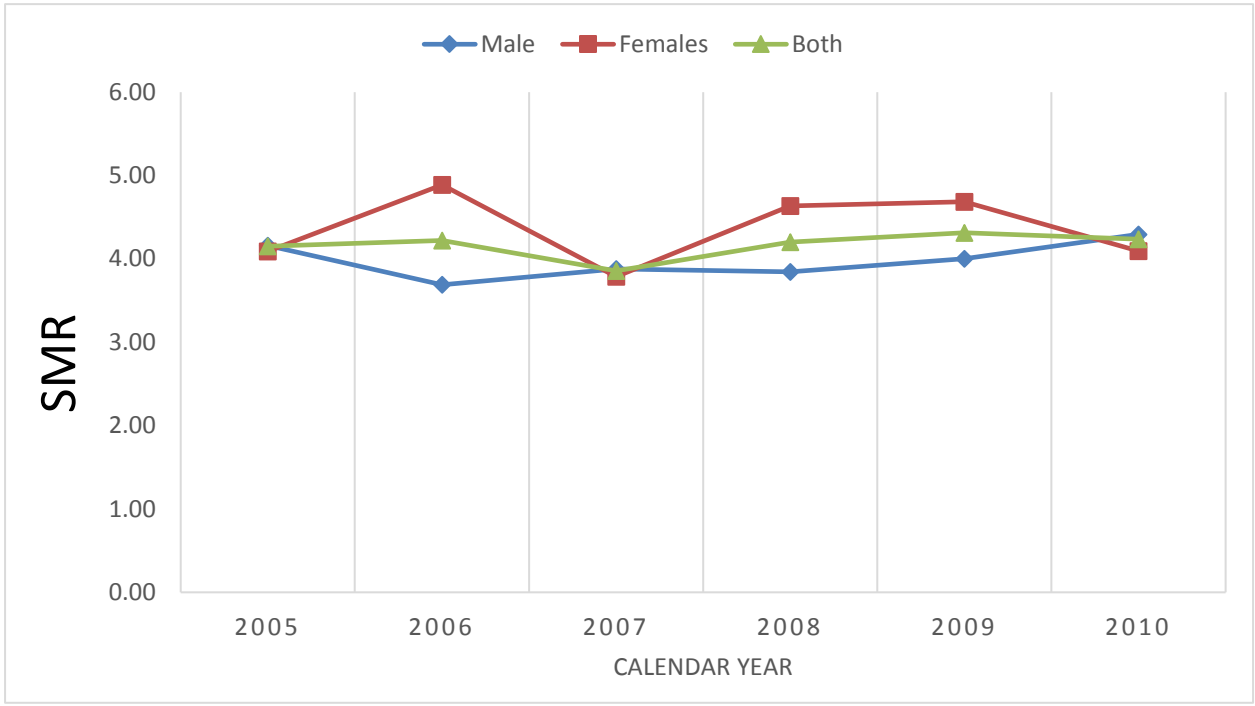


Figure 4.7 Annual Standardized Mortality Ratio (SMR) for epilepsy in Saskatchewan, Canada, 2005-2010



CHAPTER 5: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Discussion

5.1.1 Incidence

Population-based incidence studies of epilepsy are scarce in Canada. The present study measured the incidence of epilepsy in the general Canadian population without limiting the analysis by demographic characteristics (male, and RI status, and the difference in time). This study is also the first one in Canada to measure the incidence of epilepsy in specific subgroups and calculate their standardized mortality ratios. Furthermore, this study examined temporal changes in the incidence, prevalence, and mortality of epilepsy using longitudinal data, thus maximizing the sensitivity of identifying PWE over time.

5.1.1.1 Overall incidence of epilepsy

The crude and age-standardized to the 2006 Canadian population incidence rates of epilepsy in Saskatchewan, Canada were estimated to be 63 and 62 cases per 100,000 person-years respectively and were consistent with other total population studies in developed countries (range 40-70 per 100 000 person-years) (18,19).

5.1.1.2 Sex and age-specific incidence rate of epilepsy

We found a slightly higher incidence of epilepsy for men than for women. Similar variations by sex have also been found in other studies in developed countries (39, 40). The reasons behind these gender differences are not clear. One possible explanation is the higher rate of concussions among males between 16 and 34 years of age than females (115). In epilepsy, head injuries account for 20% of symptomatic epilepsy in the general population and 5% of all

epilepsy(116). The higher rate of concussions among males might explain the slightly higher incidence of epilepsy in this group compared to females.

Another factor that may contribute to the differences in the incidence of epilepsy between sexes is the higher prevalence in boys of almost all developmental disabilities (DD) (117). Some male predominant causes of DD, such as Fragile X Syndrome, have long been recognized, and are known to be associated with a higher prevalence of epilepsy (118). Other X-linked disorders resulting in intellectual disability have more recently been described (119), as advances in the field of genetics have accelerated. In many of the other causes of DD, the male preponderance is still not well understood etiologically. However, regardless of the reasons for a male preponderance in children with DD, high rates of epilepsy in DD would then naturally be expected to result in higher rates of epilepsy in males than females overall. In fact, systematic reviews have clearly established epilepsy to be the most prevalent condition (22.0 in 100) in children with DD(120), especially those with greater severity of DD. Unfortunately, patients with DD are also more likely to have hard to treat (drug-resistant) epilepsy (121–123), so their need for access to specialty epilepsy clinics is often considerable.

On the other hand, we corroborated previous findings of a low incidence rate in adulthood compared to the elderly population (36). In the pediatric population, we did not have data for patients under two years due to the diagnosis algorithm excluding this population. However, in the age group between 2 and 14 years, the incidence of epilepsy (47.7 and 42.2 per 100,000 person-years) was close to the incidence described previously in the pediatric Canadian population (46 per 100,000)(13).

5.1.1.3 Temporal changes in the incidence

There are few studies reporting incidence rates for more than one time period with the same method of case ascertainment(124). In this study, we calculated the incidence of epilepsy over six-year period in the same population with the same method of case ascertainment for the first time in Canada.

In this study, we found a significant decrease in the incidence of epilepsy over the study period. This decreased incidence has been seen previously in Iceland (38), Finland (125) and UK(53) where better perinatal and neonatal care , universal vaccination, a method of ascertainment for the diagnosis of epilepsy(drug use database), have been thought to account for this decrease (126–128).

It is difficult to attribute the decrease of epilepsy in our population to one cause alone. Epilepsy is a condition with many possible causes. Anything that disturbs the normal pattern of neuronal activity in the brain such as abnormal brain development, illness or trauma can lead to seizures (129). There are some public health measures which may prevent new cases of epilepsy in the population. They include 1) good prenatal and postnatal care related to pregnancy and postnatal care; 2) the prevention of head injury and other trauma: wearing seatbelts, use of bicycle helmets, the use of car seats for infants; 3) treating cardiovascular disease: adequate management of high blood pressure; and 4) preventing and treating effectively infection that may affect the brain during childhood and adulthood (130).

It is interesting that countries, where the incidence of epilepsy has decreased have a universal health care publicly funded system, unlike countries where the incidence of epilepsy has increased such as in the USA (36). The presence of universal health care may have led to better

public health, resulting in the reduction of diseases, healthier people, and ultimately a decrease in the incidence of epilepsy(131).

Another cause of the decreased incidence of epilepsy could have been the immigration of healthy people in those aged 20-59 (5,132) where the decreased incidence of epilepsy in Saskatchewan was noted. The migration of healthy immigrants has been well documented in Hispanic and Latino American immigrants in the U.S. where these groups tend to have comparable to or better health outcomes than those of their non-Hispanic, white counterparts(133). Information from Statistics Canada shows that the percentage of landed immigrants in Saskatchewan increased from 0.8% in 2005 (Canada 100%) to 2.7% in 2010(134). Within the 2006 Canadian census there were 48,155 immigrants in Saskatchewan, and in 2012, the interprovincial migration together with the increase in immigration added 80,000 people to the province(135). Furthermore, 58.6% people who migrated to Canada were in the core working age group between 25 and 54 years and 14.5% were between the age of 15 and 24. Children aged 14 and under accounted for the 19.4% of the newcomer population and seniors (65 and older) represent 3.3% of all arrivals (136). In summary, it is clear that the population of Saskatchewan increased mostly by immigration in the 15 and 54 age group.

5.1.1.4 Incidence in self-identified RI

There is abundant evidence that some chronic diseases such as diabetes (137), cardiovascular disease (138,139), renal disease (140), certain cancers (141,142), and respiratory diseases (143) are more frequent in the Canadian Aboriginal population than the general population. Our study demonstrated an increased incidence of epilepsy in the self-declared RI population. To our knowledge, this is the first study to link epilepsy to the list of frequent chronic diseases among the Aboriginal population.

The identification of differences in the incidence of epilepsy within different groups is crucial to the prevention of and the improvement of the overall outcome in epilepsy in a subpopulation. Populations may differ in socioeconomic circumstances, behavior, beliefs, and genetics which may result in inequalities unless these differences are taken into account. For example, a given population may have:

1. Differences in education and other socioeconomic markers in accessing healthcare
2. Difficulty in accessing healthcare in an appropriate language and cultural context
3. Different disease patterns and/or responses to therapy
4. Differences in acceptability of treatment interventions

Awareness of these differences allows focused delivery of health promotion and healthcare so that, for example, programs may increase the prevention and detection of epilepsy (such as early detection clinics) and provide effective care (144) (such as epilepsy surgery for specific focal epilepsies).

In our study, we found that the incidence of epilepsy in self-declared RI was 1.6 times significantly higher than the rest of the population. The highest incidence was seen in males and in the 55-59 age group. On the other hand, the lowest incidence of epilepsy was seen in the 80-84 group age. High incidence rates of epilepsy in RI might be explained by the high incidence of traumatic brain injuries in the indigenous population (145), which might be particularly high in males. On the other hand, we found, the lowest incidence of epilepsy was seen in the 80-84 RI group age group. The lowest rate in this oldest sub-group of RI is consistent with other studies in Native American populations, where no incident cases of epilepsy had been reported in the elderly population (50,51). We speculate that the healthy survivor effect (146) may account for this

finding, which may be even more noticeable due to inequities in the provision of healthcare services for RI resulting in earlier deaths of those with medical comorbidities. For example, elderly RI with multiple comorbidities such as diabetes and cardiovascular disease that higher likelihood of developing stroke (which is a major risk factor for epilepsy in this group) might only rarely live into the oldest age group.

Regardless of the health indicator explored, Canadian Aboriginals have been shown to suffer a disproportionate burden of illness with poor outcomes. This is generally believed to be related to their economic and social deprivation as well as long history of colonialism and marginalization (147). Despite targeted government health programs, disparities in health between the Aboriginal population and the overall Canadian population, remain (147) and we have shown that epilepsy is not an exception.

5.1.2 Prevalence

5.1.2.1 Overall prevalence

Our study identified 8,880 individuals living with epilepsy in Saskatchewan in 2010. This represents an age-standardized prevalence of 8.8 per 1,000 people (95%CI: 8.6, 9.0). The prevalence was higher in males (9.2 per 1,000 people) than in females (8.4 per 1,000 people) and highest in the 35-39 age group (12.5 per 1,000 people)

The prevalence in this study is higher than previously reported by Tellez et al. (9) with 5.2 per 1,000 people in Saskatchewan (95%CI:4.4, 6.1). This difference may be explained by the methodology used to obtain the results. In the study by Tellez, the ascertainment of epilepsy cases was self-reported and only covered the population older than 12 years old. In our study, the case

ascertainment was based on an algorithm with excellently established metrics (sensitivity and specificity of 88.9% and 92.4% respectively (107) and which also did not rely on self-identification of epilepsy. This is of particular interest in the discussion of conflicting research results. All throughout history, in practically every culture, epilepsy has been seen as something to be dreaded, avoided and disguised. Today, at least in the developed world, this has decreased although it is still in recent memory (148) and might affect self-disclosure rates.

Consistent with this, have been a number of studies indicating that patients with epilepsy themselves hold negative attitudes concerning epilepsy and that this self-image contributes to the stigma expressed by the community. For example, up to 23.4% of patients in a developed country with health record confirmed epilepsy denied having epilepsy (149).

5.1.2.2 Age-specific prevalence

The prevalence of epilepsy in this study demonstrated a trimodal pattern, with peaks in the young, middle age and the oldest. Most other studies have reported a gradual increase in epilepsy prevalence toward adolescence or early adulthood, a stable prevalence in the third and fourth decades and dropping rates after the fifth decade of life. Only a few studies in Denmark (151), USA (116) and the province of Ontario, Canada (8) have shown this trimodal pattern, as we did in the prevalence of epilepsy. In these studies the increase in prevalence in older age group could have been a reflection of the improved life expectancy of those with epilepsy due to better control of the disease, resulting in increased prevalence at older ages during this period (5).

5.1.2.2 Temporal trends of the prevalence of epilepsy

In our study, we found an increase in the prevalence of epilepsy in Saskatchewan over the six-year study period. This phenomenon has also been found in the UK, where researchers determined temporal trends in the epidemiology of epilepsy over 10 years period, finding that the prevalence of epilepsy increased in both females and males between 1983 and 1993 from 16.7 to 17 per 1,000 (53).

Our study population was a dynamic one, i.e., patients entered and left the group at different times. The increased prevalence of chronic diseases in this population, therefore, could have been due to either an increase in the incidence of the disease or higher survival rates of people with the disease (5). Our findings of decreasing incidence of epilepsy in the Saskatchewan population allowed us to conclude that the higher survival rate of patients with epilepsy is the answer to the increase in prevalence.

5.1.3 Mortality

5.1.3.1 Overall mortality and age-specific

Various measures can be utilized to evaluate mortality. The standard measures proposed by the International League Against Epilepsy (ILAE) include mortality rate, and standardized mortality ratio (SMR). The SMR is the most widely recognized measure and is used to compare rates of death among individuals with epilepsy and a referent population (94).

By 2005, there were five population-based studies of mortality in the entire epilepsy population worldwide (97). These studies (in developed countries) suggested up to threefold increases in mortality compared to the general population (SMR 1.6 to 3) and mortality rate between 4.8 and 7.8 per 100,000 person-years (97).

In this study we found that the SMR for epilepsy in Saskatchewan was up to 2.45 times higher than the general population (95%CI 2.33, 2.58) similar to results found in other developed countries. We found the highest SMR in children and the lowest was in the elderly group. These observations have been seen previously where SMRs have shown an increase with age being the reflection of both the low mortality in the reference population and the high mortality in children with epilepsy and neurodeficits (97).

5.2 Strengths and Limitations of the study

The biggest strength of this study is the excellent provincial health data system which provided the primary data files for our study. The health database allows for cross-linkage of administrative health data in a generalized province-wide manner. The data collection itself is carried out in a systematic, standardized manner (152) and because of its high level of participation and retention is highly representative of the population. Finally, because of its high quality and comprehensivess, Saskatchewan's health database system has frequently been used by other researchers, including those outside the province, and has been demonstrated in several studies to be complete and accurate (153–159).

We believe that another strength of our study was the algorithm for the case definition of epilepsy. There was a previous assessment of the validity of the algorithm for the diagnosis of epilepsy using ICD-coded inpatients claims and physician claims in the neighboring province of Alberta. This found that the use of two physicians claims or one hospitalization claim in two years period was accurate on 93% with a sensitivity of 88.9% (95% CI 85.4- 92.5) and specificity of 92.4% (95% CI 89.9- 94.9) (101).

However, there were some limitations to our study, including our case definition. For example, patients with less than two years of age were not included. Other limitations to our study resulted from the method of assigning incident cases of epilepsy by ruling out diagnoses in the six-year period of observation prior the formal study diagnosis. By the definition of epilepsy, epilepsy was considered to be resolved if the person had remained seizure–free for more than ten years and was off anti-seizure medication for at least five years (1). Therefore, it is possible that a person might have been counted as a new case (incident case) of epilepsy even if they had previously had epilepsy. Another major limitation was the absence of our dataset of a specific etiology for epilepsy, classification of epilepsy and specific causes of death.

The definition of Registered Indian status was another potential limitation, as this relied on self-report, and may, therefore, have resulted in a major number of missing cases.

Another limitation could be the short period of six years to evaluate secular trends. There is no consensus on time required to identify accurately trend changes in chronic diseases. Previous studies on secular trends for epilepsy have analyzed periods over ten years. Numerous diseases have demonstrated extraordinary changes in incidence over short periods of time, yet chronic diseases may evolve over decades.

However, these results could be preliminary data awaiting for more long-term secular trends in incidence, prevalence, and mortality of epilepsy in Canada, with the anticipation of more detailed research in the future.

Because of some of the limitations described above, results from this study should be augmented by a direct population survey to screen for potential cases of epilepsy and subsequently evaluate patients in person by an epilepsy clinician for confirmation of the diagnosis and to collect

additional information. It is also essential to develop a better understanding the meaning of seizures, convulsions, and epilepsy in particular cultural settings, exploring the language and ideas used to portray seizures and epilepsy. This could help design more culturally appropriate language in surveys as well as the approaches to screening (94).

5.3 Implications

This study is the first estimate of the incidence rate of epilepsy in the total Canadian population. It also provides the first SMR estimate for the general mortality estimate of epilepsy in Canada.

Our results have shown two main points: 1) high incidence of epilepsy among the Aboriginal population and high incidence and prevalence among the elderly population.

These results suggest the urgent need to use research, education, and improvement in access and treatment of epilepsy to prevent, delay, and treat this disease, especially in light of the increasing prevalence of the Canadian elderly and aboriginal population(160,161)

In the United States, research in epilepsy is funded at a persistently lower rate than that in Alzheimer disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, and Parkinson disease and this disparity cannot be explained by differences in the burden of these diseases in the general USA population (162). In Canada, the mandate of the Canadian Institutes of Health Research (CIHR) is to "excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system" (163). However, epilepsy is not included in the priority areas of the Neuroscience, Mental Health and Addiction (164).

Hospitals and regional health authorities in Canada and elsewhere are facing significant resource allocation challenges. Priorities based on clinical impact, community needs, and resource implications must be set among competing opportunities because demand for health care exceeds available resources (165). Epilepsy needs to be one of the high health priorities in the province of Saskatchewan.

This study, therefore, provides information about core indicators of public health and healthcare needs of the population as well as crucial inputs for the burden of epilepsy in Saskatchewan and Canada.

5.4 Conclusion

The purpose of the current study was to determine the overall incidence rate, prevalence, and mortality of epilepsy in the province of Saskatchewan, Canada describing them annually and over a period of six years and estimating their crude, age-standardized and stratum measures. In this research study, the use of administrative data from the province of Saskatchewan and the use of a previously validated epilepsy algorithm provided the necessary information to measure these key morbidity and mortality indicators in epilepsy for this Canadian province.

Although incidence, prevalence, and mortality of epilepsy have been described all around the world, Canada lacks on information on incidence and mortality in all age group, in subgroups, and over a period of time (trends). This study described for the first time the crude and age-standardized incidence of epilepsy in the province of Saskatchewan as well as the incidence of epilepsy in self-identified Registered Indian subgroup and standardized mortality ratio for epilepsy. Finally, the prevalence of epilepsy was described.

This study found that the overall and age-standardized incidence and prevalence of epilepsy were in the range reported in other developed countries empathizing a higher incidence in the elderly population. Also, the SMR was similar than previous reports. However, important differences were found in the incidence's trends and previous prevalence rates of epilepsy in Saskatchewan. This study has identified an overall decrease incidence of epilepsy over time only seen in countries with universal health care (Finland, Sweden, and the UK). However, this data is preliminary due to a short follow-up period and needs more comprehensive research in the future. On the other hand, the prevalence of epilepsy in this study is greater than the previous measure of prevalence in the province, which may be explained by the methodology used in each study.

One of the more significant findings to emerge from this study is that the incidence of epilepsy in self-declared RI is higher than the rest of the population and that the incidence of epilepsy in the elderly self-declared RI was low.

This resulted in our finding that epilepsy is the second most frequent neurological disease in Saskatchewan affecting all population groups, but especially Aboriginal and elderly populations. Its incidence is higher than multiple sclerosis (MS) (incidence of 9.5 per 100,000) (166), dementia and Alzheimer's disease (incidence of 0.73 per 100,000) (167) and its prevalence is higher than MS (prevalence of 2.8 per 1,000 people) (166), Alzheimer's (prevalence of 28 per 1,000 people) (167)and Parkinson's disease (prevalence of 2, per 1,000 people). Also, people with epilepsy died more frequently than the rest of the population.

In a health system that is facing significant resources allocation challenges, identifying health priorities is a key for success, and epilepsy has to be one of these priorities.

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