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Healthcare Utilization and Expenditure of Tuberous Sclerosis Complex Associated with Epilepsy in the United States

Esther Nkrumah
Nova Southeastern University

Healthcare Utilization and Expenditure of Tuberous Sclerosis Complex Associated with Epilepsy in the United States

Esther Nkrumah, PhD(c), MS, CCRP

Nova Southeastern University

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We hereby certify that this dissertation, submitted by Esther Nkrumah, conforms to acceptable standards and is fully adequate in scope and quality to fulfill the dissertation requirement for the degree of Doctor of Philosophy in Health Science.

_____ _____

Sarah Ransdell, PhD — Date
Chairperson of Dissertation Committee

_____ _____

Jodi Clark, MD, MPH, CWWS — Date
Dissertation Committee Member

_____ _____

Sara Knox, PT, PhD, DPT — Date
Dissertation Committee Member

Approved:

_____ _____

Brianna Black Kent, PhD — Date
Interim Program Director

_____ _____

Akiva Turner PhD, JD, MPH — Date
Chair, Department of Health Science

_____ _____

Stanley H. Wilson, P.T., Ed.D., CEAS — Date
Dean, College of Health Care Sciences

Abstract

Tuberous sclerosis complex (TSC) is characterized as a rare hereditary disorder impacting an estimated 25,000-40,000 persons in the United States and 1-2 million persons worldwide (Song et al., 2017). Individuals with TSC have extensive comorbidities that affect their health-related quality of life, healthcare utilization, and expenditure. The current literature lacks documentation on the impact of the various comorbidities and their association with healthcare utilization and expenditures among individuals with TSC. The purpose of this dissertation study was to examine the trends in healthcare utilization (emergency department and inpatient admission) and expenditures that can be identified among individuals diagnosed with TSC, with and without epilepsy. Multivariate analysis was conducted to compare the proportions of TSC patients with epilepsy to the proportions of TSC patients without epilepsy, with regards to the use of inpatient hospital (IP) care, emergency room (ER) use, and total expenditures. Among the 3,572 patients analyzed, 65.5% of the study population were TSC patients with epilepsy, compared with 34.5% of patients without epilepsy. Approximately 81% of the patients had between one to ten comorbidities and the expected primary payer for most patients (67%), was public health insurance (26% Medicare, and 40.7% Medicaid). The odds of hospital admission were nearly two-fold higher among those with epilepsy (OR and CI). This finding indicated that increased ED use among TSC patients with epilepsy may also lead to increased hospitalization. The overall mean annual expenditure for ED visits by TSC patients without epilepsy was slightly lower than that for patients with epilepsy. However, for an inpatient stay, TSC patients without epilepsy had higher total expenditures ($63,520) compared with TSC patients with epilepsy ($40,248).

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Chapter 1: Introduction

Introduction to the Chapter

Tuberous sclerosis complex (TSC) is characterized as a rare hereditary disorder impacting an estimated 25,000-40,000 persons in the United States and 1-2 million persons worldwide (Song et al., 2017). TSC affects multiple organ systems, including the brain, kidneys, lungs, heart, and skin. However, the manifestation of the disease is highly diverse and varies significantly among individuals impacted (Northrup & Krueger, 2013). This rare genetic disorder mutates in the TSC1 on chromosome 9q34 and the TSC2 on chromosome 16p13 (Toldo et al., 2019; Curatolo, Bombardieri, & Cerminara, 2006), causing benign tumors in the brain, kidneys, heart, lungs, liver, eyes, and skin (Sun et al., 2015). People with TSC have an increased risk of developing epilepsy due to the disruption of a TSC gene expression in the brain, leading to cerebellar atrophy, abnormal cellular growth, migration, and proliferation (Curatolo, 2015; Moavero, Cerminara & Curatolo, 2010). There is significant variability in the clinical presentation of TSC based on the characteristics associated with the onset of lesions coupled with neurological manifestations, such as epilepsy and neurodevelopmental disorders (Almobarak et al., 2018; Hallett et al., 2011).

Although various types of comorbidities (benign neoplasm of the kidney, malignant neoplasm of the brain, epilepsy, autism, ulcerative colitis, and mood disorders) occur in individuals with TSC, neurological disease (disorders of the nervous system) is arguably the most important clinical issue. Epilepsy is one of the most common comorbid conditions among individuals with TSC, with an onset of seizures occurring during the first year of life (Nabbout et al., 2019). Current estimates suggest 80-85% of all TSC patients develop epileptic seizures, with two-thirds who are not responsive to antiepileptic treatment (Curatolo et al., 2018; Overwater et

al., 2015; Moavero, Cerminara, & Curatolo, 2010). The multiple comorbidities associated with TSC and its effects on various organ systems indicate a significant health care and disease burden, as well as a substantial economic burden on individuals, their families, and society.

Statement of the Problem

TSC inflicts a burden on society by imposing a significant toll on both the individuals who have the condition and their families and caregivers. Individuals with TSC are at risk of poor health outcomes; however, those associated with epileptic seizures are at an even greater risk of poor health outcomes, along with constant use of health care and higher health-care costs.

The burden of disease management for TSC is well established in the literature; however, there is limited available evidence of healthcare utilization and expenditure. In a systematic review of the TSC literature, Hallett et al. (2011) concluded there is limited economic and humanistic outcome research in this population, representing an important knowledge gap in the cost of illness and treatment.

The goal of this dissertation study is to quantify and compare healthcare utilization and expenditure among individuals diagnosed with TSC with and without epilepsy. Factors including socio-economic status, clinical impact, and cost-effectiveness of treatment will be explored. More importantly, understanding the profile and cost of healthcare utilization of these individuals using real-world data is critical for (a) quantifying the existing burden on the healthcare system, (b) identifying areas of sub-standard care for various comorbidities associated with this disorder, (c) estimating future healthcare utilization and expenditures, and (d) bridging the gap in currently published literature.

Research Question

This dissertation study examined and compared healthcare utilization and expenditures among individuals diagnosed with TSC, with and without epilepsy. The central guiding questions to be examined in this study are as follows:

Question**:** What trends associated with healthcare utilization (emergency department use and inpatient admissions) and expenditures can be identified among individuals diagnosed with TSC with and without epilepsy?

Aim 1**:** To determine the healthcare utilization (inpatient and emergency department) among individuals diagnosed with TSC with and without epilepsy.

Aim 2: To determine the specific costs associated with the care of these individuals.

Aim 3: To determine the prevalence and impacts of predisposing comorbidities on hospital admissions and expenditures among individuals with TSC who are diagnosed with epilepsy.

Aim 4: To determine the socio-demographic and patient dispositions among individuals with TSC that are associated with epilepsy.

Relevance and Significance

TSC is characterized as a rare hereditary disorder impacting an estimated 25,000–40,000 persons in the United States and 1–2 million persons worldwide (Song et al., 2017). Individuals with TSC have an increased risk of developing epilepsy, which is considered as one of the most common comorbid conditions. Although seizures are a hallmark manifestation of TSC, there is a paucity of data in the public domain characterizing healthcare resource utilization and expenditure in the TSC population.

Little has been published in the last 10 years describing healthcare utilization and expenditure burden of TSC and even less for individuals with comorbid epileptic seizures. A search of the literature on healthcare utilization and expenditures of individuals with TSC associated with epilepsy resulted in locating few publications: two studies conducted in the United States, one in the United Kingdom, and one in Sweden. The absence of robust literature of direct and indirect costs associated with TSC, and specifically in conjunction with epilepsy, prevents an accurate assessment of the economic burden (Hallett et al., 2011)

Lennert et al. (2013) characterized resource utilization in a small cohort over 5 years in patients with TSC and associated seizures in the US. This study revealed that hospitalization was common in 83.2% of TSC patients, with a mean of 0.50 per year/patient and an average length of stay of 6.22 days. Furthermore, neurologic-related hospitalizations accounted for a mean number of 0.28 per year/patient and an average stay of 6.03 days (Lennert et al., 2013). A similar study conducted recently in the US to examine TSC health care utilization based on the National Inpatient Sample Database (NIS) using a dataset from the years 2000-2010 revealed that of the 5,655 patients studied, 41.2% had epilepsy and an overall median total hospitalization charge of $14,807 across all years (Wilson et al., 2016). A study conducted in the United Kingdom examining the economic burden of TSC associated with epilepsy over a 3-year period found patients incurred costs of £14,335 (U.S. equivalent of $18,449) on average, with a significant proportion of costs attributed to inpatient admissions (Shepherd et al., 2017). Lastly, a study conducted in Sweden to estimate the prevalence, manifestations, treatments, healthcare utilization, and mortality of TSC patients with epilepsy found that patients with refractory epilepsy (specifically those with infantile spasm) had the highest mean healthcare utilization (Welin et al., 2017). Other relevant TSC studies examining healthcare utilization and

expenditure include (a) a study in France by Chevreul et al. (2015) that estimated an average annual cost of EUR 22,459 (U.S. equivalent of $24,953) per patient for Systemic Sclerosis (SSc), (b) Vekeman et al.'s (2015) study in the Netherlands examining individuals with TSC associated with cyclin-dependent kinase (CKD) revealed an average expenditure of EUR 1,275-31,916 (U.S. equivalent of $ 1,566 – 39,215) annually in 2012, (c) a study in the United Kingdom by Kingswood et al. (2016) that estimated the average expenditure of £12,681(U.S. equivalent of $16,336) per person over the 3 years among individuals with TSC, and (d) a study in the United States that estimated TSC patients with subependymal giant cell astrocytoma (SEGA) had a mean expenditure of $85,397 (Sun et al., 2015), and TSC renal angiomyolipoma (AML) patients with mean total healthcare costs ranging from $29,240-$48,499 (Song et al., 2017).

The economic burden among individuals with TSC associated with epilepsy remains poorly understood, with little evidence describing how the disease-associated costs impact patients, caregivers, and society. The need for improvement in healthcare utilization and expenditure related to the management and care for these individuals is essential to promote adequate disease control and improve health and social outcomes. The findings from this dissertation study will provide public health practitioners, health care providers, policymakers, and other TSC stakeholders with healthcare utilization and expenditure data for this population. The availability of such data ensures that evidence-based programs, supportive services, and disease management meet the complex needs of individuals with TSC associated with epileptic seizures.

Definition of Terms

The following definitions of terms are important in the understanding of this dissertation study:

Epilepsy. Epilepsy is a chronic disease characterized by sudden recurrent and unprovoked episodes of neurological disturbance, loss of consciousness, and convulsions triggered by abnormal brain activity (Epilepsy Society, n.d.).

Seizure. A seizure is a sudden surge of electrical activity in the brain that usually affects how an individual appears or acts for a brief period (Epilepsy Foundation, n.d.). According to the epilepsy foundation, there are variations with the nature of seizures. These variations are due to the particular lobe of the brain which controls different behaviors, movements, and experiences (Epilepsy Foundation, n.d.).

Health Disparity. Health disparity is defined by the Centers for Disease Control and Prevention as preventable differences caused by the burden of disease, poverty, environmental threats, inadequate access to health care, and lack of opportunities to achieve optimal health (CDC.gov, n.d.).

Healthcare Utilization. Healthcare utilization is the measure of a population's use of healthcare services such as utilization of hospital resources, personal home care resources, and physician resources available to them (Manitoba Center for Health Policy, n.d.).

Socio-Economic Status (SES). SES is considered as the social standing or class (educational level, income, and occupation) of an individual or group (American Psychological Association, n.d.).

International Classification of Diseases, Ninth Revision (ICD-9). ICD9 is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

Summary of the Chapter

This chapter introduced the research problem and gaps in the literature regarding healthcare utilization and expenditure in TSC patients with epilepsy. It also presented the research questions to be explored, highlighted the study's implications for healthcare providers and public policy, and described the importance of access to evidence-based data to aid supportive services and disease management to meet the needs of the individuals impacted by TSC.

Chapter 2: Review of the Literature

Introduction to the Chapter

This literature review chapter presents an introduction to tuberous sclerosis complex and epilepsy, a theoretical framework, and existing research that underpins the basis for this dissertation study.

Tuberous Sclerosis Complex (TSC)

TSC was first described by von Recklinghausen when he presented a full-term stillborn infant whose brain contained several sclerotic areas post-partum in 1862 (Roach, 2016). Eighteen years later, a researcher named Bourneville characterized a baby's brain pathology as "sclérose tubéreuse des circonvolution cérébrales," the name used to describe the disorder (Roach, 2016). Bourneville in 1980 used the term "tuberous sclerosis of the cerebral convolutions" when describing the potato-like appearance of the cerebral lesion observed (Curatolo, Moavero, & de Vries, 2015).

TSC is considered one of the most common neurocutaneous disorders involving multiple organ systems (DiMario, Sahin, & Ebrahimi-Fakhari, 2015). It presents variably during infancy, childhood, and early adulthood in all ethnic groups and both sexes (DiMario, Sahin, & Ebrahimi-Fakhari, 2015). This rare genetic disorder results in the mutation of the TSC1(encoding hamartin) gene on chromosome 9q34, and TSC2 (encoding tuberin) gene on chromosome 16p13 (Toldo et al., 2019), causing benign tumors in the brain, kidneys, heart, lungs, liver, eyes, and skin (Sun et al., 2015). Mutations in the TSC1 or TSC2 gene lead to disruption of the TSC1-TSC2 intracellular protein complex (Curatolo et al., 2015), causing overactivation of the mammalian target of rapamycin (mTOR) protein (responsible for the coordination of several facets of cell functioning, including cell growth, metabolism, and proliferation; Slowinska et al.,

2018). mTOR, is a serine/threonine kinase found in two distinct complexes, mTOR complex 1(mTORC1) and mTOR complex 2 (mTORC2; Curatolo at al, 2015). mTORC1 regulates protein synthesis, gene transcription, and cell cycle progression and survival, while mTORC2 has a role in mediating cytoskeletal dynamics (Franz & Capal, 2017). Abnormalities associated with the mTOR pathway are believed to contribute to the development of many cancers, TSC, and other neurologic disorders (Franz & Capal, 2017). Mutations in the TSC1 gene account for 10% of TSC cases, while the TSC2 gene is associated with an estimated 90% of the clinical cases (Crino et al., 2006).

Prevalence, Clinical Characteristics, and Diagnosis of TSC

The occurrence of tuberous sclerosis complex is estimated to be as high as 1:5,800 live births with a high mutation rate of 1:250,000 per gene, per generation (Northrup et al., 1999 [Updated 2018]). The population prevalence of TSC is estimated to be about 25,000-40,000 persons in the United States and 1-2 million persons worldwide (Song et al., 2017).

The clinical features of TSC manifest differently from person to person and are highly variable and age-dependent (Roach, 2016). Although neurological and neuropsychiatric manifestations (manifestations in the brain, seizures, intellectual disability, developmental delay, and psychiatric illness) are the major sources of morbidity and mortality, most patients present clinical findings of various comorbid manifestations (Curatolo et al., 2015). Tumors occurring in the central nervous system (CNS) are among the leading causes of mortality and morbidity in TSC patients (Northrup et al., 1999/2020). These brain tumors, found in TSC patients include subependymal nodules (SENs), which occur in 80% of individuals, cortical dysplasia, occurring in 90% of individuals, and subependymal giant cell astrocytomas (SEGAs), occurring in 5-15% of all individuals (Northrup et al., 1999/2020]). Seizures affect more than 75% of TSC patients,

and about 50% have a developmental delay or intellectual disability (Curatolo et al., 2018; Kingswood et al., 2017). Neuropsychiatric manifestations present in most individuals with TSC are characterized as tuberous-sclerosis-associated neuropsychiatric disorders (TAND; Curatolo et al., 2015). TAND includes manifestations that are behavioral, intellectual, and psychosocial. Individuals with TSC are also at high risk for autism spectrum disorder (ASD), with recent estimates of 16 - 61% (Kingswood et al., 2017)

Non-neurological manifestations, including dermatological manifestations (the appearance of hypomelanotic macules (90%), angiofibromas (75%), fibrouscephalic plaques (25%), ungual fibromas (20%), shagreen patches, and confetti skin lesions) are often the first sign of TSC (Curatolo et al.,) with the skin affected in all TSC patients (Northrup et al, 1999 [Updated 2020]). In addition, cardiac rhabdomyomas, which occur in 60% of individuals with TSC are considered to be part of the initial identifiable manifestations of the disorder and can play a major role in the diagnosis of TSC (Curatolo et al., 2015). Manifestations in the kidney (angiomyolipomas, cysts, renal cell carcinomas); heart (rhabdomyomas, arrhythmias); and lungs (lymphangioleiomyomatosis, multifocal micronodular pneumonocyte hyperplasia) are other non-neurological manifestations present in individuals with TSC (Northrup et al, 1999/2018). Table 1 illustrates the various clinical characteristics and comorbidities associated with TSC.

Table 1

Clinical Characteristics and Comorbid manifestations associated with TSC

Organ System	Clinical Manifestation	Definitions	Clinical Findings
Skin	Hypomelanotic macules	Characterized as ("ash leaf spots") patches of skin that may appear anywhere on the body and are caused by a lack of melanin.	Hypomelanotic macules are estimated to occur in approximately 90% of individuals with TSC (Northrup et al, 1999/2018).
	Confetti skin lesions	Stippled hypopigmentation, typically on the extremities. Characterized by red papules on the malar region.	Confetti skin lesions occurs in 3% to ≤58% (Northrup et al, 1999/2018).
	Facial angiofibromas	An irregularly shaped, slightly elevated soft skin-colored patch, usually on the lower back, made up of excess fibrous tissue.	Facial angiofibromas occur in approximately 75% of individuals with TSC (Northrup et al, 1999/2018).
	Shagreen patches	Nodular or fleshy lesions that arise adjacent to or from underneath the nails.	Shagreen patches occur in approximately 50% of individuals with TSC (Northrup et al, 1999/2018).
	Ungual fibromas	Fibrous growths that are located around the fingernails or toenails	Ungual fibromas occur in 20% overall but ≤80% in older affected adults (Northrup et al, 1999/2018).
Central Nervous System (CNS)	Subependymal nodules (SENs)-	Small nodular masses which originate in the subependymal region of the lateral ventricles and protrude into the ventricular cavity.	Northrup & Krueger (2013), estimate the prevalence of SENs to occur in 80% of individuals with TSC.
	Cortical dysplasias	Malformation of the cerebral cortex due to improper migration of neurons in utero.	Cortical dysplasias affect approximately 90% of individuals with TSC (Northrup & Krueger, 2013).

	Subependymal giant cell astrocytomas (SEGAs)	Tumors commonly located within the ventricles of the brain.	SEGAs are estimated to occur in 5%-20% of all individuals with TSC (Kothare et al. 2014).
	Epileptic Seizure	A sudden, uncontrolled electrical disturbance in the brain.	An estimate of >80% of individuals with TSC has been reported to have seizures (Northrup et al, 1999/2018).
	TSC-Associated Neuropsychiatric Disorder (TAND)	Characterized by the manifestation of brain dysfunction such as; behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties.	An estimated 90% of individuals with TSC exhibit TAND features (de Vries et al. 2018).
	Autism Spectrum Disorder (ASD)	A developmental disorder that affects communication and behavior.	Approximately 16% to 61% of individuals with TSC develop characteristics of ASD with disease manifestation occurring as early as the age of nine months (Kingswood et al 2017
Kidneys	Angiomyolipomas	Characterized as a benign tumor of the kidney, can grow such that kidney function is impaired.	Renal disease occurs in an estimated 80% of individuals with TSC. Angiomyolipomas and cysts are the most common pathology observed (Rakowski et al. 2006).
	Renal Cystic disease	Characterized by the development of numerous fluid-filled cysts in the kidneys.	Clinically detectable renal cystic disease occurs in approximately 50% of patients with TSC (Dixon, Hulbert & Bissler, 2010).
Heart	Cardiac rhabdomyomas	A common primary tumor of the heart in infants and children that degenerates over time and eventually disappear.	Approximately 47%-67% of individuals with TSC presents Cardiac rhabdomyomas (Northrup et al, 1999/2018).

Lung	Lymphangioleiomyomatosis (LAM)	Pulmonary disorder that typically presents in early adulthood	LAM is estimated to occur in approximately 34% of females with TSC (Moss et al., 2001)
Eye	Retinal hematomas	Typically, asymptomatic and are not progressive, but they may obstruct vision in some patients	Retinal hematomas are estimated in approximately 50% of individuals with TSC (Rosser, Panigrahy & McClintock, 2006).

A diagnosis of TSC can be made after careful clinical examination coupled with selected organ imaging, laboratory testing, and genetic evaluation (DiMario, Sahin, & Ebrahimi-Fakhari, 2015). The criteria for TSC diagnosis were revised at the International TSC Consensus Conference in 2012. The primary mode of diagnosis includes a genetic criterion as well as clinical features. According to the revised diagnosis criteria (Table 3), a definitive diagnosis of TSC can be made in the presence of a pathogenic TSC1 or TSC2 mutation, and a possible diagnosis is made when either 1 major feature or greater than 2 minor features are present (Curatolo et al., 2015). The presence of specific disease symptoms is rare; however, individuals with TSC present several common characteristics that require further investigation, such as (a)identification of family member with TSC, (b) identification of cardiac rhabdomyomas, (c) postnatal identification of hypopigmented macules on the skin, and (d) the development of seizure (DiMario et al., 2015).

Table 2

Diagnostic criteria according to the International Tuberous Sclerosis Complex Consensus Conference

Diagnostic criteria for TSC
Definite diagnosis: presence of a pathogenic TSC1 or TSC2 or two major clinical features
Possible diagnosis: presence of either 1 major feature or greater than 2 minor features

Major Criteria / Features

Skin/oral cavity	Hypomelanotic macules (n>3, at least 5 mm diameter)
	Angiofibromas (n>3) or fibrous cephalic plaque
	Ungual fibromas (n>2)
	Shagreen patch
Central Nervous System	Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)
	Subependymal nodules
	Subependymal giant cell astrocytoma
Heart	Cardiac rhabdomyoma
Lungs	Lymphangioleiomyomatosis
Kidney	Angiomyolipomas (n>2)
Eyes	Angiomyolipomas (n>2)

Minor Criteria / Features

Skin/oral cavity	“Confetti” skin lesions
	Dental enamel pits (n>3)
	Intraoral fibromas (n>2)
Kidney	Multiple renal cysts
Eyes	Retinal achromic patch
Other organs	Nonrenal hamartomas

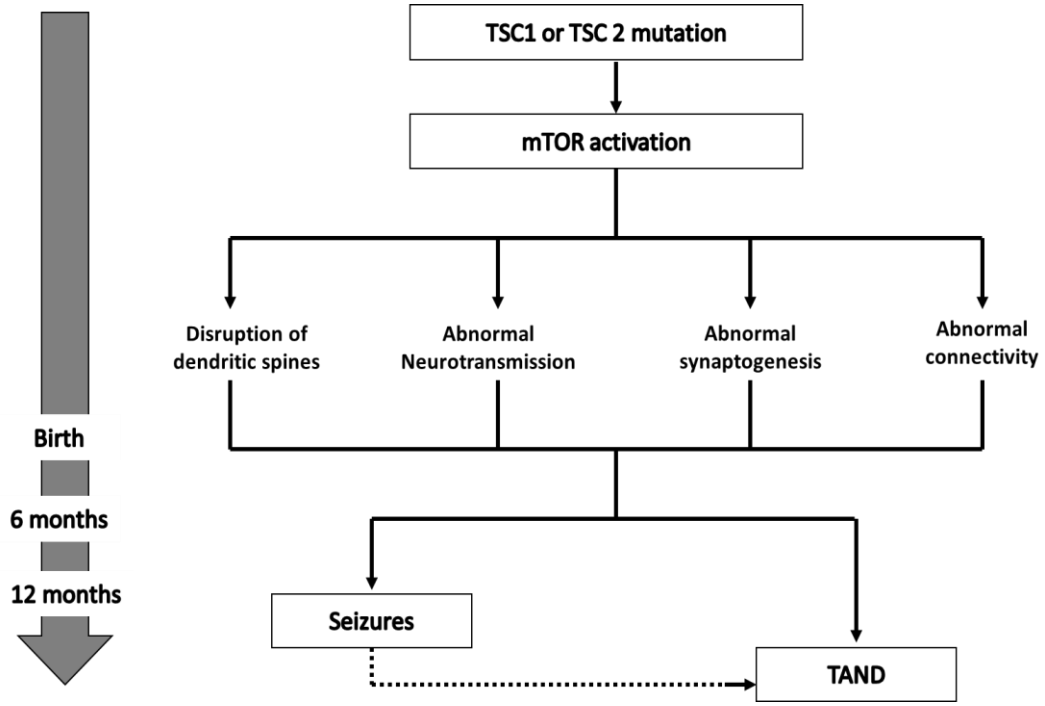
Tuberous Sclerosis Complex and Epilepsy

Epileptogenesis is a chronic process by which a normal brain, often triggered by genetics or acquired factors, develops epilepsy (Curatolo et al., 2018). The presence of cortical tubers

(dysplastic neurons, giant balloon cells, and glial components) are attributed to the development of epilepsy in individuals with TSC (Jeong & Wong, 2016). Experimental studies suggest a mutation of the TSC gene along with mTOR overactivation (Fig 1), resulting in the early appearance of refractory seizures, TAND, and the encephalopathic process (Curatolo et al., 2018).

Figure 1

TSC-associated seizures and TAND



Adapted from, Curatolo, P., Nabbout, R., Lagae, L., Aronica, E., ……. Jóźwiak, S. (2018). "Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations." European Journal of Paediatric Neurology.

Epileptic seizures affect 80-85% of individuals with TSC and are the most common neurological comorbidity, with a significant incidence of morbidity and mortality (Almobarak et

al., 2018; Nabbout et al., 2019). These seizures are not sudden occurrences, but rather a progressive change that can be detected early in life through EEG synchronization and appearance of focal or multifocal epileptiform activity (Cusmai et al., 2011). Clinical investigations by researchers have indicated a high incidence of abnormalities in EEG patterns and epileptiform features (Thiele, 2014). Experimental studies have suggested that the early onset of epileptic seizures and the severity of the seizures may be attributed to a deficiency of GABAergic interneurons, delayed GABA excitation, disruption of GABAergic interneuron migration, and/or alterations in GABA-A receptors (Cusmai et al., 2011). While many types of seizures are seen in individuals with TSC, infantile spasms are the most common and often manifest during the first year of life (Curatolo et al., 2018). Other manifestations of epilepsy in TSC patients include focal to bilateral tonic-clonic, atypical absence, myoclonic, and generalized tonic-clonic seizures (Almobarak et al., 2018).

Diagnosis of Tuberous Sclerosis Complex Associated with Epilepsy

The diagnosis of TSC as accepted and recommended by the Tuberous Sclerosis Consensus Conference in 2012 is based on the emergence of a pathogenic mutation (present in 75-90% cases) in either TSC1 or TSC2 gene (Slowinska et al., 2018). Other diagnostic criteria for TSC include the presence of cardiac rhabdomyomas, dermatological findings with hypomelanotic macules, ophthalmological changes, and renal manifestations (Slowinska et al., 2018). In a large TSC registry study conducted by Ebrahimi-Fakhari et al. (2018), the median age of diagnosis was one year. In most individuals, the diagnosis of TSC is made after the onset of seizures (Slowinska et al., 2018). A study conducted by Jeong and Wong (2016) demonstrated that brain activity characterized by cortical tuber hamartomas was linked to an increased risk of epilepsy in individuals with TSC. Ebrahimi-Fakhari et al. (2018) found that

CNS involvement with seizure disorders was the most common clinical symptom at diagnosis of TSC and had a prevalence rate of 69.8%. Lastly, Chung et al. (2017) explained that the presence of interictal epileptiform discharges (patterns of activity between seizures) and electrographic seizure activity on EEG are precursors to the onset of seizures in individuals with TSC.

Treatment of Epilepsy Associated with Tuberous Sclerosis Complex

Individuals with TSC are at risk of poor health outcomes; those with epileptic seizures have an even higher risk. The goal of epilepsy treatment in individuals with TSC is to prevent the occurrence of seizures, thus maximizing the opportunity to improve cognitive development and overall quality of life (Curatolo et al., 2018; Curatolo, Jozwiak, & Nabbout, 2012). Treatment of epilepsy in individuals with TSC is considered difficult despite the availability of several options in the management of the disease. A study conducted by Song et al. (2019) reported that nearly all (92.3%) of the patients in the study received non-surgical and/or surgical treatment for the management of epileptic seizures, with 99.5% receiving antiepileptic drugs (AEDs). This study also reported a large proportion of patients who initiated multiple AEDs, corroborating an earlier study by Overwater et al. (2015) that reported more than half of all patients studied had refractory (uncontrolled or drug-resistant) epilepsy.

Although epilepsy treatment in individuals with TSC is refractory for most, treatment options tend to be similar to those for non-TSC-associated diagnoses, including the use of AEDs as well as nonpharmacologic approaches. AEDs such as topiramate, lamotrigine, carbamazepine, valproic acid, and levetiracetam have all been found to be effective and well-tolerated in this population (Canevini et al., 2018). Nonpharmacologic options include surgery, ketogenic diet, and vagus nerve stimulation (Song et al., 2018; Curatolo, Jozwiak, & Nabbout. 2012).

Pharmacologic Treatment Options

Antiepileptic drugs are commonly used in the management of epilepsy in TSC and are considered to be first-line therapy (Song et al., 2018). Current literature indicates that one-third of the children with TSC develop infantile spasms (Canevini et al., 2018), a rare epileptic disorder that occurs in young children. The International TSC Consensus Conference, a panel of TSC experts, recommended vigabatrin (VGB) as the first-line therapy for infants and AEDs with c-aminobutyric acid (GABA)ergic mechanisms for older children (Overwater et al., 2015). In a study conducted by Marques et al. (2019), the most common treatment for TSC patients with epilepsy was GABAergic agents (e.g., vigabatrin), both in mono and combination therapy. Vigabatrin, an inhibitor of GABA transaminase, is considered to be the most effective AED in infants with spasm and other seizures (Canevini et al., 2018; Jozwiak et al., 2011). Other AEDs such as valproic acid, levetiracetam, clobazam, lamotrigine, topiramate, oxcarbazepine, carbamazepine, and adrenocorticotropic hormone have all been found to be effective in treating epileptic seizures in individuals with TSC (Marques et al., 2019; Overwater et al., 2015). In an open-label prospective patient chart review conducted by Overwater et al. (2015), the most commonly used AEDs in TSC were valproic acid (85%), vigabatrin (61%), levetiracetam (46%), carbamazepine (41%), and clobazam (41%). Literature from emerging studies also suggests that the mechanistic target of rapamycin (mTOR) inhibitors may improve seizure and developmental outcomes in TSC patients (Marques et al., 2019; Chung et al., 2017). mTOR activation can result in increased neuroexcitability and seizures, thus mTOR inhibitors such as sirolimus (rapamycin) and everolimus work by inhibiting mTOR signaling events (Curatolo et al., 2018). Results from a randomized control trial conducted by French et al. (2016) to investigate everolimus therapy for treatment-resistant seizures associated with TSC showed a significant

reduction in seizure frequency and improvement in seizure control. Although there are various AEDs available for the treatment of epilepsy in individuals with TSC, many of these individuals develop seizure disorders that are pharmacoresistant. Table 3 illustrates the various pharmacologic treatment options for individuals with TSC associated with epilepsy.

Table 3

Pharmacologic options for *treatment of epilepsy associated with Tuberous Sclerosis Complex*

Drug	Drug Class	Indication	Treatment Recommendation
Vigabatrin	Anti-epileptic, Gamma amino acids and derivatives	For use in treatment resistant epilepsy, refractory complex partial seizures, and secondary generalized seizures.	Monotherapy in TSC related spasm or focal seizures.
Adrenocorticotropic Hormone (ACTH gel)	Carboxylic acids and derivatives	For treatment and management of seizure disorders such as infantile spasm	Monotherapy for TSC-related infantile spasm.
Everolimus	Protein Kinase inhibitor, Antineoplastic Agent	For the treatment of TSC associated with seizures	Adjunctive treatment of adult and pediatric patients aged 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures
Valproic acid	Anticonvulsants	For treatment and management of seizure disorders such as absence seizures, tonic-clonic, and complex seizures.	Monotherapy and adjunctive therapy for complex partial seizures that occur either in isolation or in association with other types of seizures
Levetiracetam	Anticonvulsants, Carboxylic acids, and derivatives	Used to treat partial-onset seizures in adults and children who are at least 1 month old	Adjunctive therapy in the treatment of partial-onset seizures in adults and children 4 years of age and older with epilepsy.

Carbamazepine	Anticonvulsant, Benzazepines	Used for the treatment of partial or complex partial seizures	Adjunctive therapy in both children and adults.
Clobazam	Benzodiazepines, Anticonvulsant.	For treatment and management of epilepsy and seizures associated with Lennox-Gastaut syndrome, a difficult-to-treat form of childhood epilepsy.	Adjunctive therapy in patients 2 years and older.
Lamotrigine	Anticonvulsants, Benzene, and substituted derivatives	Used either alone or in combination with other medications to treat epileptic seizures in adults and children.	Adjunctive therapy for seizures in patients ≥2 years of age and monotherapy in adults with partial seizures.
Oxcarbazepine	Anticonvulsant, Carboxamide	Anticonvulsant drugs used primarily for the treatment of epilepsy.	Monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy.
Topiramate	Anticonvulsant, Anti-epileptic, Dioxolopyrans	Used for the treatment of epilepsy in children and adults.	Monotherapy for partial-onset or primary generalized in patients over 2 years of age. Adjunctive therapy for partial-onset seizures adults.

Non-Pharmacologic Treatment Options

The evaluation of nonpharmacologic options early during treatment is important due to the refractory nature of AEDs among patients with epilepsy. Nonpharmacologic epilepsy treatments shown to be effective in patients with TSC are the ketogenic or low glycemic index diet, epilepsy surgery (Overwater et al., 2015), and vagus nerve stimulation (Connolly, Hendson, & Steinbok, 2006).

Epilepsy Surgery. Surgical treatment of epilepsy in children and adults with TSC has gained significant interest in recent years, although surgical management proves to be complex and challenging. The complexities are due to challenges associated with epileptogenic tuber complexes merging subtly with each other, and involvement of more than one region of the brain (Gupta, 2017). The effectiveness of epilepsy surgery has been shown in patients with refractory epilepsies, with seizure freedom achieved in 50-60% of patients (Fohlen et al., 2018). This is consistent with a systematic review of literature by Jansen et al. (2007) that showed the successful outcome of epilepsy surgery in patients with drug-resistant epilepsy and tuberous sclerosis. Among these patients, the authors concluded that seizure freedom was achieved in 57% of the patients, and seizure frequency improved by >90% in 18% of patients (Jansen et al., 2007). A long-term study conducted by Liang et al. (2017) also reported satisfactory seizure freedom in 74.5% of the patients with TSC one year after surgery, 58.8% at five years after surgery, and 47.8% ten years after surgery. To ensure better outcomes and seizure improvement in TSC patients, candidates for epilepsy surgery should be carefully selected based upon a comprehensive imaging and electrophysiological data, as well as invasive EEG recordings to ensure the accurate identification of epileptogenic zones (Fohlen et al., 2018).

Ketogenic Diet. The ketogenic diet as a treatment for epilepsy and seizure control has been documented in the medical literature for over 80 years. New variations of the ketogenic diet have emerged in the last decade, including the modified Atkins diet and the low-glycemic-index diet. The ketogenic diet can be an effective option in the management of epilepsy in patients with TSC, particularly younger patients for whom surgery is not appropriate (Kossoff et al., 2018; Martin-McGill et al., 2018; Curatolo et al., 2012). The ketogenic diet has been shown to have the ability to reduce mTOR activation in animal models, thus providing a scientific basis

for its mechanism of action in TSC-associated seizures (Curatolo, 2018). Liu et al. (2018) reported evidence of significant positive outcomes with the ketogenic diet for the treatment of refractory epilepsy. In this study, analysis of patients with drug-resistant epilepsy showed that the ketogenic diet was effective with 13% of the patients achieving seizure freedom and over 50% of the patients achieving seizure reduction by more than 50%. Similarly, a randomized controlled trial conducted by Ijff et al. (2016) showed a positive cognitive and behavioral effect of the ketogenic diet in children and adolescents with refractory epilepsy. For clinical management of seizures, the ketogenic diet has been highly recommended for individuals and specifically children who have failed more than two antiseizure medications (Kossof et al., 2018).

Vagus Nerve Stimulation (VNS). VNS is a common neuromodulation based intervention in patients with inadequately controlled seizures (Gonzalex, Yengo-Kahm, & Englot, 2019). It is approved as an adjunctive therapy by the U.S. Food and Drug Administration (FDA) for use in individuals 4 years and older with intractable partial-onset seizures. There is limited literature regarding the use of vagus nerve stimulation in individuals with tuberous sclerosis and refractory seizures. However, VNS has been proven to be an effective and safe treatment for intractable epilepsy (Zamponi et al., 2010). In a small cohort study of individuals with TSC, Parain et al. (2001) demonstrated the efficacy of using VNS as a mechanism for seizure control. A similar study conducted by Elliott et al. (2009) in a small cohort of 19 patients with refractory epilepsy and TSC further supports the use of VNS as a safe and effective treatment option. In this study, 82% of the patients experienced a 67% reduction in seizures (Elliott et al., 2009).

Theoretical Framework

TSC disease etiology, manifestation, and treatment are well documented in the literature. However, there is a scarcity of available evidence for healthcare utilization and expenditure in this population. This dissertation study used a modified Anderson's model of healthcare utilization and its theoretical framework to determine the factors that contribute to healthcare utilization and costs associated with illness and treatment.

Andersen's model has been used extensively and is important in understanding the reasons for excess healthcare utilization and expenditures when comparing groups of patients. For the purpose of this study, the main constructs from Anderson's model to be used include environment, population or patient characteristics, and health service use. The use of healthcare services among individuals with TSC with or without epilepsy (i.e., ED visits, inpatient hospitalizations) and healthcare expenditures (i.e., expenditures for ED visits and inpatient hospitalizations) was examined. A modified version of Anderson's model for this dissertation study is shown in Figure 2. The framework to be examined includes predisposing factors, enabling factors, individual-specific healthcare needs, healthcare utilization, and costs (Anderson, 1995; Graves, 2009).

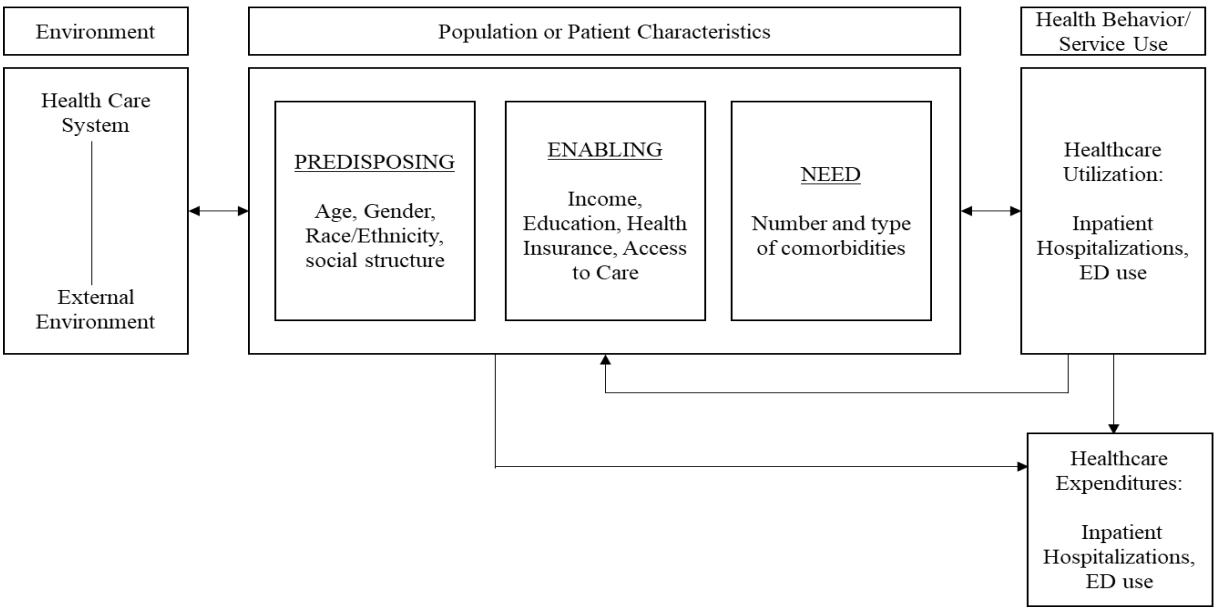
Predisposing factors are socio-cultural characteristics (social structure, health beliefs, and demographic factors) that exist before an illness (Anderson, 1995). When examining healthcare utilization, it is important that enabling resources such as health facilities and health personnel are available within the communities where people live and work (Anderson, 1995). Measures such as health insurance and income are important factors when analyzing enabling resources for healthcare utilization. Aday and Anderson (1974) explained that the framework for examining access to care can be conceptualized as a process that includes an assessment of health policies

(financing, education, and organization), characteristics of the healthcare system, the population at risk to the utilization of the health services being rendered, and consumer satisfaction.

Among the predisposing factors, age and gender were examined in this dissertation research. Insurance coverage (insured and uninsured), the health status of the patient, income, and accessibility to care were also examined as enabling factors. Measures of need included individual medical needs and perceived severity of the medical needs (co-existing comorbidities). Healthcare utilization and costs of services, such as inpatient hospitalizations and emergency department visits, are factors used to explain differences in outcomes (healthcare utilization and expenditures) for individuals with TSC with and without epilepsy.

Figure 2

Modified Anderson Behavioral Model



Adapted from, Anderson, R. M. (1995). Revisiting the behavioral model of access to medical care: Does it matter? Journal of Health Care and Social Behavior, 36, 1-10.

Summary of the Chapter

The results of this literature review were congruent. Healthcare utilization and expenditure in individuals with TSC and epilepsy are complex and not well-studied. Treatment of TSC associated with epilepsy is considered difficult despite the availability of several options in the management of the disease. Anderson's model of healthcare utilization and its theoretical framework were used to determine the factors that contribute to healthcare utilization and costs associated with illness and treatment.

Chapter 3: Methodology

Introduction to the Chapter

Estimating the economic burden associated with TSC can be challenging, due to the complexity of the disease, including the diversity of the patient population and the heterogeneity in the clinical disease manifestation, coupled with the existence of various comorbidities. This chapter presents the methodology, research design, institutional review board (IRB) application and approval process, and reliability and validity of the study, including information regarding the data collection process, data preparation, and the strategy for data analysis.

Research Design

The research described in this dissertation was performed as a retrospective, cohort study, to assess the differences in healthcare utilization and expenditures among individuals diagnosed with TSC with and without comorbid epilepsy, in the United States. Five years of data, obtained from the Nationwide Emergency Department Sample (NEDS), was used for this study. Each ED visit included up to 15 diagnosis codes, based on the International Classification of Disease, 9th revision, Clinical Modification (ICD–9–CM). According to the ED records, all patients with a diagnosis of TSC (ICD 9-CM code 759.5) and epilepsy (ICD 9-CM code 345), in any position, between 2010-2014 were abstracted.

Baseline characteristics, including each patient's sociodemographic information and comorbidities, were extracted, and the outcomes (healthcare utilization and expenditures) were measured. All utilization rates and adjusted healthcare costs for the TSC population sample were compared against those for patients with epilepsy as a comorbidity. The direct costs were determined based on the total healthcare expenditures and derived from the sum of all direct payments made for all healthcare services.

Institutional Review Board and Data Use Agreement

An institutional review board (IRB) application was submitted to the Nova Southeastern University IRB, and approval was received. After the receipt of IRB approval, data collection and extraction were initiated. The Agency for Healthcare and Research Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) nationwide Data Use Agreement (DUA) was completed before receiving access to the NEDS data set.

Resources and Data Collection

This dissertation examined current trends in healthcare utilization (for both the emergency department and inpatient admissions) and expenditures among individuals diagnosed with TSC, both with and without epilepsy, using data from the NEDS database. The data files are publicly available for download and use. NEDS data are distributed as fixed-width, ASCII-formatted data files. The NEDS database represents one of the largest all-payer ED databases, containing national estimates for hospital-based ED visits, and was created as part of the AHRQ Healthcare Cost and Utilization Project [Healthcare Cost and Utilization Project (HCUP), 2011]. NEDS contains information from approximately 28 million ED visits, at 980 hospitals, providing a 20%-stratified sample of U.S. hospital-owned EDs. NEDS contains geographic, hospital, and patient characteristic information, as well as data regarding the nature of hospital visits (e.g., common reasons for ED visits, acute and chronic conditions, and injuries), and discharge information. The data are compiled from hospital billing records, from both state emergency department databases (SEDDs) and state inpatient databases (SIDs). SIDs include information regarding individuals who are initially treated in the ED and are subsequently admitted to the same hospital. SEDDs contain information regarding those ED visits that do not result in hospital admissions (i.e., treat-and-release visits and transfers to another hospital).

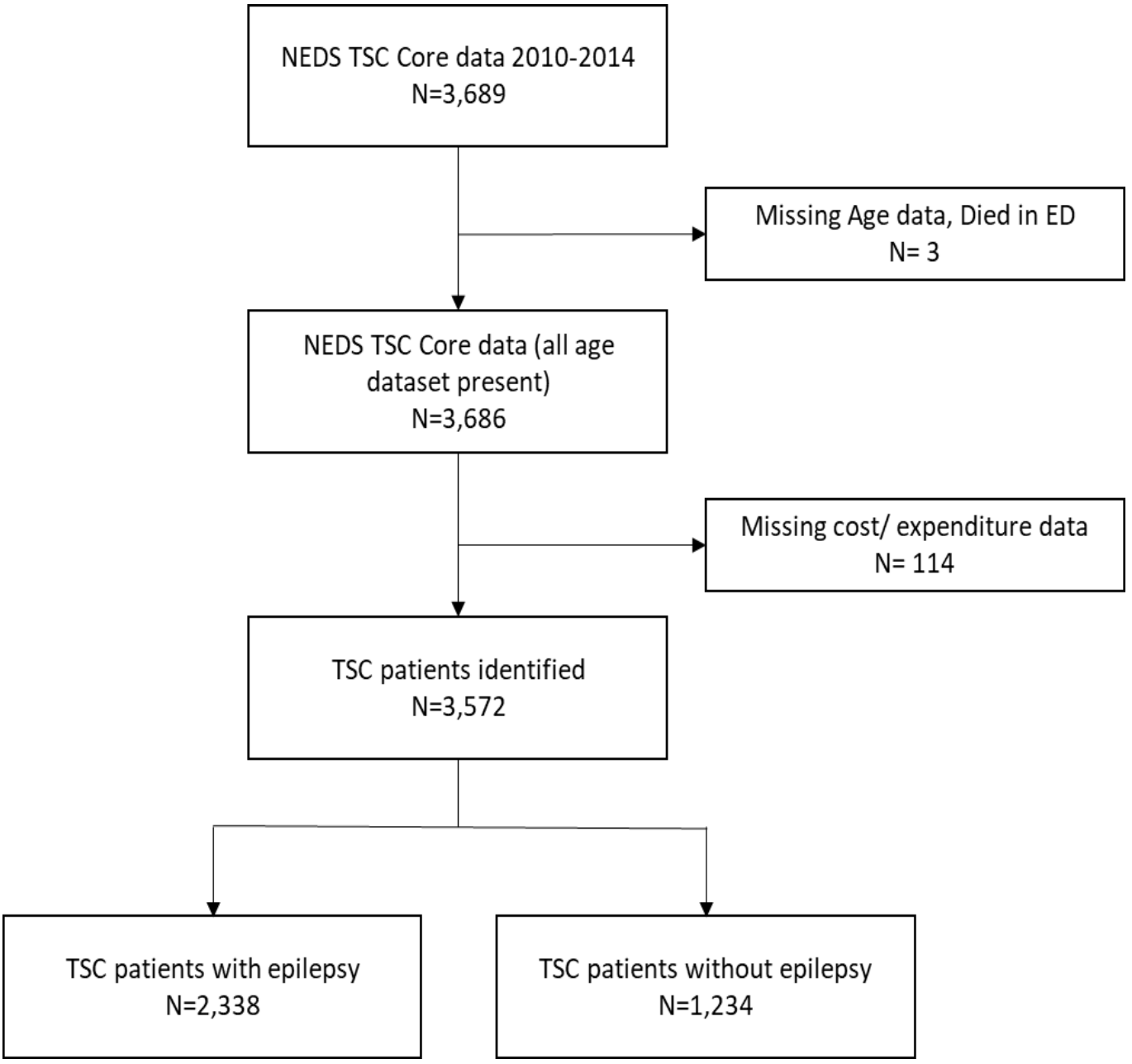
These data facilitated the estimation of resource utilization associated with a relatively rare condition. Using databases, such as NEDS, can help understand the extent and pattern of inpatient and ED use among TSC patients and provides additional information regarding the reasons for such visits, including the primary diagnosis received during the ED visit and the outcome of the ED visit (e.g., treated and released, transfer to home health, or inpatient hospitalization). An analysis of these data allowed associations among TSC, healthcare utilization, and healthcare costs, to be inferred, using a previously unused method.

Identification of the Study Sample

The data used in this study were obtained from the NEDS database. TSC patients were identified using the ICD 9-CM code 759.5. Data from the years 2010-2014 were obtained and relevant dataset extracted. The NEDS core data files, which contain records for 100 percent of ED visits, were linked with the NEDs supplemental inpatient file. A unique NEDS record identifier (KEY_ED) can be used to link a patient's NEDS core file with the corresponding supplemental inpatient file. The inclusion criterion for this study was patients with TSC; therefore, all patients with a TSC diagnosis (ICD 9-CM code 759.5) were included in this study. Patients were excluded if the following data fields were missing from the dataset; age, gender, and total cost/charges. Figure 3 presents a flow diagram showing how the sample was identified. A total of 3,689 individuals met the inclusion criterion. After applying the exclusion criteria, a final sample of 3,572 patients was identified.

Figure 3

Identification of the study sample



Reliability and Validity

For quantitative research, Creswell (2014) explained that employing accuracy verification can result in meaningful interpretations of the data. For this dissertation research, the standards used to stratify the data and the data collection methods will assure the data quality. To ascertain the reliability of the data files, the NIS utilized a systematic sampling design to construct the database. This sampling design was a self-weighted sample design, similar to random sampling methods. The self-weighted sample design is considered to be efficient because it ensures that the sample is representative of the population, based on several critical factors, including hospital factors (hospital-unidentified, census division, ownership, urban-rural location, teaching status, number of beds) and patient factors (diagnosis-related group, admission month). In addition, a systematic sampling design reduces the margin of error for estimates. The NEDS data is based on a stratified probability sample of hospital-owned EDs.

Data Analysis

SPSS version 24 was used for all statistical analyses. A descriptive analysis of the TSC patient samples with and without epilepsy was performed. Continuous and categorical variables were summarized using means and percentages, respectively. Multivariate analysis was conducted to compare the proportions of TSC patients with epilepsy to the proportions of TSC patients without epilepsy, with regards to the use of inpatient hospital (IP) care, emergency room (ER) use, and total expenditures. The healthcare utilization of TSC patients, both with and without epilepsy, was assessed by calculating the differences in the mean annual frequency of healthcare services during the study period, for each type of service. The epilepsy-specific direct healthcare costs were estimated as the differences in healthcare expenditures for all service types between TSC patients with epilepsy and those without epilepsy. To measure the relationships

among categorical variables, chi-square analyses were used (inpatient hospital admissions and emergency room use), whereas t-tests were used to assess continuous outcome variables (length of stay and annual expenditures) for the sub-group analyses of mean differences between TSC patients with and without epilepsy. Based on the conceptual framework applied in this study, the dependent variables will focus on the use of healthcare services among TSC patients with and without epilepsy, including the number of ED visits, the number of inpatient hospitalizations, and healthcare expenditures for ED visits and inpatient hospitalizations.

Variables of Interest

Dependent variables

TSC and epilepsy diagnoses were identified in NEDS, using the Clinical Classifications Software (CCS) diagnosis codes, which were reported for each ED visit. The CCS is based on the ICD-9-CM system, the accepted clinical mechanism for the identification of diagnoses and claim submissions, which are tied to insurance reimbursement. The CCS maps ICD-9 codes (which are extracted from the clinical ED encounter discharge abstract) with nearly 260 clinically meaningful diagnosis categories (Table 4). The CCS diagnosis code was selected as the preferred variable for identifying TSC and epilepsy diagnoses for this analysis, based on clinical applications and analytical feasibility. Although NEDS provides ICD-9-CM codes for up to 15 diagnoses per emergency department visit, we used only the first diagnosis listed for this analysis. Senathirajah et al. (2011) explained that the first-listed diagnosis for an emergency department record indicates the code for the diagnosis, condition, problem, or other reason for an encounter/visit shown in the medical record that is thought to be chiefly responsible for the services provided. Other dependent measures of utilization include trends for ED visits and hospital inpatient days.

NEDS provides information regarding the charges for ED and inpatient services, which was used to identify the economic burden associated with ED visits and inpatient stays. Total ED charges included both ED visits that resulted in "treated and released" patient outcomes and ED visits that resulted in hospitalization at the same hospital. The total charges were adjusted for inflation, relative to the value of the US dollar in 2014. To calculate the inflation adjustment factor, the annual consumer price index (CPI) was utilized to transform/convert the total charges into 2014 constant dollars. The CPI was obtained from the Bureau of Labor Statistics (Bureau of Labor Statistics, US Department of Labor, 2019).

Table 4

ICD-9-CM Code Categorization

Category	CCS Code
Psychiatric	650-670
Cancer	11-47
Cardiovascular Disease	53, 96-118, 213
Endocrine Disease	48-52, 55, 58
Gastrointestinal Disease	135, 138-146, 148-155, 214
Respiratory Disease	122- 134
Infectious Disease	1-10, 76
Rheumatology	54, 201-206, 210
Pulmonary	56, 116
Autoimmune Disease	57
Hematologic Disease	59-64
Nervous System Disease	77-85, 94-95, 216, 227

Ophthalmologic Disease	86-93
Vascular Disease	119-121
Nephrological Disease	156-166, 215
Gynecological /Obstetrics	167-196, 218-224
Dermatological Disease	197-200
Injury	226-236, 239-240

ICD-9-CM, International Classification of Disease, 9th revision, Clinical Modification; CCS, Clinical Classification Software

Independent variables

Gender (male and female) and age (all ages reported) were selected as the predisposing independent variables, based on the Anderson-Aday model. Age was categorized into infant (< 1 year), pre-school (1–5 years), grade-school (6–9 years), pre-adolescent (10–13 years), adolescent (14–17 years), and adult (> 18 years) groups. Enabling variables included the health insurance coverage reported as the primary payer for both the ED and inpatient stay (categorized as Medicare, Medicaid, private, self-pay, no charge, or other) and socioeconomic status (median household income for the patient's zip code, assigned by HCUP). The disposition status from the ED was also examined, categorized as discharged (patients treated and released from the ED), admitted (patients admitted to the same institution), or other (transferred, left against medical advice, died in the ED). The numbers and type of comorbidities reflected the need variables from the model.

Summary of Chapter

This chapter described the data set that was used during this dissertation research and how the research population was identified. This chapter also described the research measures

and operationalization of variables and provided a profile of the study population and the analytical methods used to test and answer the proposed research questions and aims.

Chapter 4: Results

Introduction to the Chapter

This chapter presents the results of the statistical analyses performed to assess differences in the health service utilization and expenditures between TSC patients with epilepsy and those without epilepsy, as well as other predisposing, enabling, and need characteristics. This chapter also presents the results of multivariate analysis, which was used to test the hypotheses and identify the factors associated with health service utilization and expenditures.

Description of the Study Population

Tables 5 and 6 presents the characteristics of the study population, in terms of predisposing (age, gender, and TSC diagnoses), enabling (expected primary payer), need (number of comorbidities), and health behavior/service use (the type of ED event and disposition from ED) factors. As shown in Table 5, among the 3,572 patients analyzed, 65.5% of the study population were TSC patients with epilepsy, compared with 34.5% of patients without epilepsy. Among the study population, 1,755 (49.1%) were men and 1,818 (50.9%) were women. Most patients (60.4%) in the study population were adults (age > 18 years), whereas 7.3% were adolescents (age 14-17 years), 5.7% were pre-adolescent (age 10-13 years), 7.4% were grade school children (age 6-9 years), 14.6% were pre-school children (age 1-5 years), and 4.6% were infants (< 1 year). Approximately 81% of patients had between one and ten comorbidities, 17% had between ten and twenty comorbidities, and 2.1% had greater than twenty-one comorbidities. Over half of the patients, 1,829 (51.2%), were treated and released from the ED after their initial hospital encounter. In contrast, 1,609 (45%) of patients were admitted to the same hospital during their initial ED visit. The expected primary payer for most patients (67%) was public health insurance (26% Medicare and 40.7% Medicaid), whereas private insurance accounted for 26%. Patient location was

categorized based on the urban-rural classification scheme for U.S. counties, developed by the National Center for Health Statistics (NCHS), which emphasizes the distinction and differentiation of counties associated with large metropolitan areas (counties near metro areas with populations ≥ 1 million), separating these counties into two categories; large, "central" metro (akin to inner cities) and large, "fringe" metro (akin to suburbs). Other NCHS classifications include medium metropolitan, small metropolitan, micropolitan, and counties that are neither metropolitan nor micropolitan. Approximately 31% (1,091) of patients lived in large, central, inner-city metropolitan areas, 25% (897) lived in large suburban metropolitan areas, and 23% (808) lived in medium metropolitan areas. Table 5 also presents the characteristics associated with the median household income for patients, based on their zip codes. As shown in this table, the patient distributions according to median household income were similar, with 891(25.2%) patients categorized in the 0–25th percentile (poorest population), 912 (25.8%) patients in the 26–50th percentile, 913 (25.9%) patients in the 51–75th percentile, and 774 patients in the 76–100th percentile (the wealthiest population).

Table 5

Characteristics of the Study Population

	N	%
All PREDISPOSING	3,572	100.0
TSC Patient with Epilepsy	2,338	65.5
TSC Patient without Epilepsy	1,234	34.5
Age (years)		
Infant (< 1)	164	4.6
Pre-School (1–5)	520	14.6
Grade School (6–9)	265	7.4
Pre-Adolescent (10–13)	204	5.7
Adolescent (14-17)	262	7.3
Adult (18+)	2,157	60.4

Gender		
Male	1,754	49.1
Female	1,818	50.9
Number of Co-Morbid Diagnoses		
1-10 Diagnosis	2,891	80.9
11-20 Diagnosis	606	17
>21 Diagnosis	75	2.1
Number of Procedures on ED Inpatient Record		
1-5 procedures	828	23.2
6-10 procedures	72	2.0
>11 procedures	10	0.3
Type of ED Event		
ED visit in which the patient was treated and released	1,829	51.2
ED visit in which the patient was admitted to the same hospital	1,609	45.0
ED visit in which the patient was transferred to another short-term hospital	124	3.5
ED visit in which the patient was not admitted to the same hospital, destination unknown	10	0.3
Disposition from ED		
Routine	1,756	49.1
Transfer to short-term hospital	124	3.5
Transfer to other: includes Skilled Nursing Facility, Intermediate Care Facility, Home Health Care (HHC)	61	1.7
Against medical advice (AMA)	12	0.3
Admitted as an inpatient to this hospital	1,609	45.0
Not admitted to this hospital, destination unknown	10	0.3
Expected Primary Payer		
Medicare	930	26.0
Medicaid	1,455	40.7
Private insurance	922	25.8
Self-pay	134	3.8
No Charge /Other	126	3.6
Patient Location: NCHS Urban-Rural Code		
"Central" counties of metro areas with ≥1 million population	1,091	30.6
"Fringe" counties of metro areas with ≥1 million population	897	25.2

Counties in metro areas with populations of 250,000–999,999	808	22.7
Counties in metro areas with populations of 50,000-249,999	326	9.1
Micropolitan counties	258	7.2
Not metropolitan or micropolitan counties	176	4.9
Median Household Income for the Patient's Zip Code		
0-25th percentile	891	25.2
26th to 50th percentile	912	25.8
51st to 75th percentile	913	25.9
76th to 100th percentile	774	21.9

ED, Emergency department

The primary reasons and diagnoses (Table 6) reported for the initial hospital encounter varied; however, more than one in five (26.1%) patients were diagnosed with epilepsy. Other notable reasons or diagnoses associated with the initial ED visit included congenital anomalies (6.0%), septicemia (2.9%), headache (2.5%), and pneumonia (2.5%).

Table 6

Primary Diagnosis at Initial Visit

	N	%
Epilepsy; convulsions	933	26.1
Other congenital anomalies	216	6.0
Septicemia	102	2.9
Headache; including migraine	89	2.5
Pneumonia	89	2.5
Fluid and electrolyte disorders	78	2.2
Urinary tract infections	72	2.0
Other nervous system disorders	69	1.9
Abdominal pain	69	1.9
Other upper respiratory infections	61	1.7
Complication of device; implant or graft	60	1.7
Fever of unknown origin	58	1.6
Other gastrointestinal disorders	58	1.6
Nausea and vomiting	53	1.5

Other injuries due to external causes	53	1.5
Nonspecific chest pain	48	1.3
Open wounds of head; neck; and trunk	48	1.3
Superficial injury; contusion	45	1.3
Aspiration pneumonitis; food/vomitus	44	1.2
Other lower respiratory disease	41	1.1
Other connective tissue disease	39	1.1
Complications of surgical procedures or medical care	35	1.0
Mood disorders	35	1.0
Schizophrenia and other psychotic disorders	32	.9
Skin and subcutaneous tissue infections	32	.9

Characteristics Associated with Epilepsy

The characteristics of the study population, according to the presence or absence of epilepsy diagnosis, are presented in Table 7. Among the study population, 65.4% (n = 2,338) had at least one claim associated with an epilepsy diagnosis, whereas 34.5% (n = 1,234) had no history of epilepsy diagnoses. Medicaid was the expected payor for the majority of TSC patients with epilepsy and among all patients. The proportion of individuals with epilepsy was slightly higher (35.2 %) among males than among females (30.2%). Similarly, epilepsy diagnoses occurred more frequently (37.2%) among adults than among all other age groups. TSC patients with epilepsy demonstrated a significantly higher number of comorbidities compared with those without epilepsy. Specifically, 52.6% of TSC patients with epilepsy had an average of one to ten comorbid condition, whereas 11.8% had eleven to twenty comorbid conditions, and 1% had more than twenty-one comorbid conditions, as compared with 28.3% of TSC patients without epilepsy with an average of one to five comorbid condition, 5.2% with ten to twenty comorbid condition, and 1.1% with greater than twenty-one comorbid conditions. Overall, the prevalence

of diseases associated with the central nervous system was higher among the study population than other comorbidities. Specifically, 38.9% of patients with epilepsy had a comorbid disease of the central nervous system. Respiratory diseases also had a high prevalence among the study population, although to a lesser extent than neuronal conditions. The total number of surgical procedures was significantly higher (66.9%) among TSC patients with epilepsy than among TSC patients without epilepsy (33.3%).

Logistic regression was performed to ascertain the effects of age and gender on the likelihood that the participants will have epilepsy. As shown in Table 7, age and gender were associated with increased odds of epilepsy diagnosis. The model was able to explain 39.0% of the variance in epilepsy diagnosis and correctly classified 65.4% of cases. Both age (except for pre-school children aged 1-5 years) and gender were significant cofactors ($P < .001$). Females had a 1.7-fold increase in the odds to experience epilepsy compared with males.

Table 7

Characteristics of the Study Population by Epilepsy Status

	TSC without Epilepsy		TSC with Epilepsy		Logistic Regression on Epilepsy		
	N	%	N	%	Sig	OR	95% CI
ALL PREDISPOSING	1,234	34.5	2,338	65.4			
Age (years)							
Infant (<1)	63	1.8	101	2.8			
Pre-School (1-5)	140	3.9	380	10.6	.479	0.888	(0.639–1.234)
Grade School (6-9)	74	2.1	191	5.3	.000	1.675***	(1.352–2.074)
Pre-Adolescent (10-13)	56	1.6	148	4.1	.003	1.541**	(1.159–2.047)
Adolescent (14-17)	74	2.1	188	5.3	.007	1.563**	(1.132–2.157)
Adult (18+)	827	23.2	1,330	37.2	.002	1.553**	(1.168–2.064)
Gender							
Male	495	13.9	1,259	35.2			
Female	739	20.7	1079	30.2	.000	1.725***	(1.498–1.986)
Primary Payer							

Medicare	303	8.5	627	17.7
Medicaid	434	12.2	1,021	28.6
Private Insurance	374	10.5	548	15.4
Self-Pay	70	2.0	64	1.8
No Charge/Other	50	1.4	76	2.1
Number of Comorbid Diagnoses				
1-10 Diagnoses	1,012	28.3	1,879	52.6
11-20 Diagnoses	184	5.2	422	11.8
>21 Diagnoses	38	1.1	37	1.0
Primary Diagnosis Classification				
Cancer	44	1.7	27	1.0
Cardiovascular Disease	84	3.2	58	2.2
Central Nervous System Disease	89	3.4	1,029	38.9
Dermatological Disease	23	0.9	25	0.9
Endocrine Disease	24	0.9	85	3.2
Gastrointestinal Disease	79	3.0	106	4.0
Infectious Disease	50	1.9	83	3.1
Nephrological Disease	72	2.7	88	3.3
Ophthalmologic Disease	34	1.3	33	1.2
Psychiatric	57	2.2	89	3.4
Respiratory Disease	176	6.6	194	7.3
Number of Procedures on ED Inpatient Record				
1-5 Procedures	263	28.9	565	62.1
>6 Procedures	40	4.4	42	4.8
Median Household Income for Patient's Zip Code				
0-25th percentile	306	8.7	585	16.6
26th to 50th percentile	334	9.5	578	16.4
51st to 75th percentile	298	8.4	615	17.4
76th to 100th percentile	273	7.7	501	14.2

Sig, significance; OR, odds ratio; 95% CI, 95% confidence interval. $p < .05$, **$p < .01$, and ***. $p < .001$.

Health Service Utilization

Health service utilization consisted of the use of inpatient services, the length of stay among those with at least one inpatient admission, and the use of the emergency room. Among the study group (Table 8), 51.2% (n = 1,829) had an initial hospital encounter in the ED, from which they were treated and released, whereas 45.0% (n=1,609) were admitted as an inpatient to the same hospital. A chi-square test of independence was performed, to examine the associations between gender, age, and the outcome of ED visits according to epilepsy status. The association between age and ED visit outcome was significant [X(5) = 37.4, $p < .001$]. Similarly, the relationship between gender and ED visit outcome was also significant [X(1) = 22.3, $p < .001$]. Among the patients who were admitted as inpatients, the majority were adults (48.6%). The proportion of TSC patients with epilepsy who were admitted to the same hospital during their initial ED encounter was higher (32.7%) than the proportion of TSC patients without epilepsy (12.3%).

Table 8

ED visit Outcomes

	TSC without Epilepsy		TSC with Epilepsy		
	N	%	N	%	Sig
ALL PREDISPOSING	1,234	34.5	2,338	65.5	
ED visit in which the patient is treated and released	764	21.4	1,065	29.8	
Sex					***
Male	312	17.1	554	30.3	
Female	452	24.7	511	27.9	
Age (years)					***
Infant (<1)	36	2.0	30	1.6	
Pre-School (1-5)	113	6.2	207	11.3	
Grade School (6-9)	53	2.9	114	6.2	
Pre-Adolescent (10-13)	43	2.4	87	4.8	

	Adolescent (14-17)	58	3.2	113	6.2	
	Adult (18+)	461	25.2	514	28.1	
ED visit in which the patient is admitted to this same hospital		441	12.3	1,168	32.7	
Sex						***
	Male	173	10.8	643	40	
	Female	268	16.7	525	32.6	
Age						***
	Infant (<1)	25	1.6	63	3.9	
	Pre-School (1-5)	20	1.2	133	8.3	
	Grade School (6-9)	18	1.1	64	4.0	
	Pre-Adolescent (10-13)	11	0.7	59	3.7	
	Adolescent (14-17)	14	0.9	67	4.2	
	Adult (18+)	353	21.9	782	48.6	

Note: * = p < .05, **p < .01, and *** = p < .001. Sig, significance; ED, Emergency department

Table 9 compares inpatient admissions according to epilepsy status and the various characteristics of the study population. Hospitalization was common among all patients; however, a high proportion (72.6%) of hospitalized patients was observed among those with epilepsy than among those without epilepsy.

To test the hypothesis that TSC patients with epilepsy are more likely to experience an inpatient hospital admission than those without epilepsy, a logistic regression analysis was performed. Table 9 presents the results of the logistic regression model for inpatient admissions. The multivariate analysis substantiated the initial observations that patients with epilepsy were more likely to experience a hospital admission, which was significant for grade school children, adolescents, and adults ($P \leq .05$). The odds of hospital admission were nearly twice as high among those with epilepsy compared with those without epilepsy.

Table 9

Inpatient Admissions by Epilepsy Status

	TSC without Epilepsy		TSC with Epilepsy		Logistic Regression on Inpatient Admission		
	N	%	N	%	Sig	OR	95% CI
ALL	441	27.4	1,168	72.6			
PREDISPOSING							
Age (years)							
Infant (<1)	25	1.6	63	3.9			
Pre-School (1-5)	20	1.2	133	8.3		1.138	(0.704-1.838)
Grade School (6-9)	18	1.1	64	4.0	.***	3.002	(1.845-4.883)
Pre-Adolescent (10-13)	11	0.7	59	3.7		1.605	(.937-2.748)
Adolescent (14-17)	14	0.9	67	4.2	**	2.421	(1.257-4.665)
Adult (18+)	353	21.9	782	48.6	**	2.160	(1.198-3.895)
Gender							
Male	173	10.8	643	40.0			
Female	268	16.7	525	32.6	***	1.897	(1.518-2.372)

Note: * = p < .05, **p < .01, and *** = p < .001. Sig, Significance; OR, Odds ratio; 95% CI, 95% confidence interval

Length of Inpatient Stay

Table 10 compares the inpatient length of stay, according to epilepsy status and the characteristics of the study population. Overall, TSC patients with epilepsy had a mean length of stay of 4.94 days, compared with a mean length of stay of 6.76 days among those without epilepsy. A significant difference between groups was determined by an independent-samples t-test. The results showed that the 1.82 day difference in the mean length of stay was significant [95% CI-825, 2.81; $t(1750) = 3.59$, $P < .001$].

To test the hypothesis that TSC patients with epilepsy would experience a longer average length of stay than those without epilepsy, a regression analysis was performed (Table 10). The

results of the regression analysis revealed that the length of stay for patients with epilepsy was shorter than that for those without epilepsy. Both gender and age (6-8years old, 14-17 years old. and 18 years and older) were significantly associated with length of stay ($P \leq .05$).

Table 10

Length of Stay Among Hospitalized Patients

	TSC without Epilepsy		TSC with Epilepsy		Logistic Regression on LOS		
	Mean	N	Mean	N	Sig	OR	SE
All	6.76	501	4.94	1251			
Epilepsy***							
PREDISPOSING							
Age (years)							
Infant (<1)	6.81	26	3.74	66			
Pre-School (1-5)	3.26	34	3.41	151		1.180	(0.737-1.889)
Grade School (6-9)	10.76	21	4.93	73	***	2.017	(1.362-2.987)
Pre-Adolescent (10-13)	2.21	14	4.1	68	*	1.684	(1.016-2.792)
Adolescent (14-17)	6.88	17	4.28	75	**	2.221	(1.233-4.000)
Adult (18+)	7	389	5.44	818	**	2.062	(1.200-3.544)
Gender							
Male	9.43	191	5.21	688			
Female	5.11	310	4.6	563	***	2.067	(1.668-2.561)

Note: * p < .05, **p < .01, and *** p < .001. Sig, significance; OR, Odds ratio; SE, standard error

Total Expenditures by Status

The total expenditures per person were transformed to a logarithmic scale and standardized in constant dollars, using 2014 as the base year, to control for inflation associated with medical care costs (Bureau of Labor Statistics, 2019). The results are presented in 2014 constant US dollars.

Tables 11 and 12 compare the mean annual expenditures for ED and inpatient stays (in 2014 constant dollars), according to epilepsy status and predisposing, enabling, and need characteristics. Annual expenditures include the amounts paid by Medicaid, Medicare, private

insurance, self-pay, and others. The overall mean annual expenditure for ED visits (Table 11) by TSC patients without epilepsy was $2,345.51, compared to $2,433.17 for TSC patients with epilepsy. An independent-samples t-test was performed to examine the mean difference in annual expenditures for ED visits between TSC patients with and without epilepsy, which showed that the mean ED expenditure difference of $87.67 was not significant [95% CI -198.94, 374.28; $t(3285) = 0.60$; $P = .549$]. TSC patients under the age of 18 who had epilepsy experienced larger ED expenditures than those without epilepsy. The population with the largest annual expenditures were patients with epilepsy whose primary classification diagnosis was cardiovascular disease. These individuals spent approximately $6,000 annually, which was more than twice the overall mean expenditure of $2,345-$2,433. High expenditures were also observed for patients without epilepsy who also had a diagnosis of cardiovascular disease ($3,851), although these patients spent less than their epileptic counterparts. Other diagnoses associated with high expenditures included rheumatological conditions and conditions of the central nervous system. For those individuals without epilepsy, gastrointestinal diseases were also associated with high costs. Medicare and self-pay patients incurred higher costs than patients using other methods of payment.

Table 11

Annual Emergency Department Expenditures According to Epilepsy Status

	TSC without Epilepsy			TSC with Epilepsy		
	Mean ($)	N	%	Mean ($)	N	%
All	2,345.51	1,153	35.1	2,433.17	2,134	64.9
PREDISPOSING						
Age (years)						
Infant (<1)	1,123.80	57	1.7	2,371.57	97	3.0
Pre-School (1-5)	1,414.85	128	3.9	1,736.20	351	10.7
Grade School (6-9)	1,551.40	69	2.1	1,910.71	174	5.3
Pre-Adolescent (10-13)	1,888.29	53	1.6	2,406.65	129	3.9
Adolescent (14-17)	2,157.21	65	2.0	2,499.77	174	5.3

Adult (18+)	2,704.06	781	23.8	2,708.90	1209	36.8
Gender						
Male	2,106.10	450	13.7	2,454.46	1155	35.1
Female	2,498.76	703	21.4	2,408.06	979	29.8
Expected Primary Payer						
Medicare	2,763.28	287	8.7	2,770.90	584	17.8
Medicaid	1,820.03	402	12.2	2,130.12	922	28.1
Private Insurance	2,555.06	347	10.6	2,575.22	495	15.1
Self-Pay	2,759.91	67	2.0	2,796.79	60	1.8
Other	2,163.12	41	1.2	2,350.99	68	2.1
Primary Diagnosis Classification						
Cancer	2,456.84	39	1.6	1,721.15	25	1.0
Cardiovascular Disease	3,851.35	79	3.3	6,033.04	50	2.1
Central Nervous System Disease	2,665.84	84	3.5	2,518.33	927	38.3
Dermatological Disease	1,477.91	20	0.8	2,661.63	19	0.8
Endocrine Disease	2,341.88	22	0.9	2,197.08	79	3.3
Gastrointestinal Disease	2,891.52	74	3.1	2,224.36	96	4.0
Infectious Disease	1,724.51	48	2.0	1,872.42	78	3.2
Nephrological Disease	2,538.80	69	2.9	2,299.46	79	3.3
Ophthalmologic Disease	2,137.88	33	1.4	1,011.22	31	1.3
Psychiatric	2,090.61	53	2.2	1,882.75	82	3.4
Respiratory Disease	1,812.22	160	6.6	1,891.37	179	7.4
Rheumatology	2,933.82	22	0.9	2,759.38	11	0.5

Note: * = p < .05, **p < .01, and *** = p < .001.

For inpatient stays (Table 12), TSC patients without epilepsy had higher total expenditures ($63,520) compared with TSC patients with epilepsy ($40,248). An independent-samples t-test was performed to determine whether a significant mean difference in annual expenditures existed for inpatient stays between TSC patients with and without epilepsy. The results showed a mean inpatient expenditure difference of $23,272.37, which was significant [95% CI -12567.24, 33977.50; $t(1740) = 4.26$, $P < .001$]. Among the study population, males without epilepsy experienced the highest total expenditures. Similarly, grade school children (6-9 years) without epilepsy had a larger inpatient expenditure ($133,524) than all other age groups. High expenditures were also observed among infants without epilepsy ($99,202). TSC patients without epilepsy who had primary diagnoses of cancer ($151,710) and infectious disease

($166,726) had the greatest total expenditures. These individuals' costs were more than double the mean expenditure of $40,248–$63,520. High expenditures were also observed among patients with epilepsy with diagnoses of cancer ($94,542) and infectious disease ($75,305), although to a lesser extent than their non-epileptic counterparts. Medicare and Medicaid patients without epilepsy incurred higher costs than all other patients in the study population.

Table 12

Annual Inpatient Expenditures According to Epilepsy Status

	TSC without Epilepsy			TSC with Epilepsy			
	Mean ($)	N	%	Mean ($)	N	%	Sig
All	63,520.45	497	28.5	40,248.08	1245	71.5	***
PREDISPOSING							
Age (years)							
Infant (<1)	99,202.13	25	3.01.4	37,224.87	65	3.7	
Pre-School (1-5)	41,177.48	34	2.0	31,744.97	151	8.7	
Grade School (6-9)	133,524.08	20	1.1	38,283.38	73	4.2	
Pre-Adolescent (10-13)	17,525.91	14	0.8	41,826.48	68	3.9	
Adolescent (14-17)	59,155.03	17	1.0	42,510.97	75	4.3	
Adult (18+)	61,416.27	387	22.2	41,904.73	813	46.7	
Gender							
Male	95,261.03	190	10.9	39,607.38	685	39.3	
Female	43,876.45	307	17.6	41,031.79	560	32.1	
Expected Primary Payer							
Medicare	77,279.81	157	9.0	39,859.69	421	24.2	
Medicaid	70,342.45	128	7.4	41,376.04	486	27.9	
Private Insurance	51,559.69	170	9.8	36,120.85	266	15.3	
Self-Pay	41,180.82	22	1.3	57,757.45	28	1.6	
Other	42,697.84	16	0.9	45,953.32	43	2.5	
Primary Diagnosis Classification							
Psychiatric	32,900.91	20	1.4	28,892.22	50	3.5	
Cancer	151,710.42	38	2.7	94,542.66	25	1.8	
Cardiovascular Disease	46,541.98	51	3.6	43,468.60	37	2.6	
Endocrine Disease	19,370.55	20	1.4	21,808.86	59	4.1	
Gastrointestinal Disease	47,911.71	37	2.6	46,437.73	73	5.1	
Respiratory Disease	45,692.21	86	6.0	46,248.71	130	9.1	
Infectious Disease	166,726.95	37	2.6	75,305.78	71	5.0	
Central Nervous System Disease	34,143.43	18	1.3	32,992.34	495	34.7	

Nephrological Disease	32,626.64	33	2.3	29,286.93	58	4.1

Note: * = p < .05, **p < .01, and *** = p < .001. Sig, significance

Summary of Chapter

This chapter presented the results of the analyses examining the characteristics associated with TSC patients with and without epilepsy, health service use, and expenditures. Bivariate analyses showed a higher proportion of patients with epilepsy used inpatient and emergency room services compared with those without epilepsy. However, the length of stay was longer among those who did not have epilepsy. The non-epilepsy group had higher mean expenditures associated with inpatient stays than those with epilepsy. A larger proportion of epileptic TSC patients experienced CNS comorbidities than non-epileptic patients.

Chapter 5: Discussion & Conclusion

Introduction to the Chapter

This chapter presents a summary of the dissertation study findings, a discussion of the findings, the relationship between this study and those reported in the existing literature, and the important conclusions that can be drawn from this study. This chapter also presents the implications for policy and practice, recommendations for further research, and the limitations, and delimitations of this study. The present study examined the healthcare utilization and expenditures associated with individuals diagnosed with TSC, comparing those with and without epilepsy. Using a modified Behavioral Model for healthcare utilization as a conceptual framework, the present study analyzed the healthcare utilization and expenditures data for TSC patients with and without epilepsy, obtained from the Nationwide Emergency Department Sample (NEDS). The study aimed to examine, analyze, quantify, and compare the healthcare utilization and expenditures of individuals diagnosed with TSC, with and without epilepsy, in the United States, using data obtained from the NEDS database.

Discussion

This dissertation study addressed the following questions regarding healthcare utilization and expenditures among individuals diagnosed with TSC, with and without epilepsy:

Question: What trends associated with healthcare utilization (emergency department use and inpatient admissions) and expenditures can be identified among individuals diagnosed with TSC, with and without epilepsy

Aim 1**:** To determine the healthcare utilization (inpatient and emergency department) among individuals diagnosed with TSC, with and without epilepsy.

Aim 2: To determine the specific costs associated with the care of these individuals.

Aim 3: To determine the prevalence and impacts of predisposing comorbidities on hospital admissions and expenditures among individuals with TSC who are diagnosed with epilepsy.

Aim 4: To determine the sociodemographic and patient dispositions among individuals with TSC that are associated with epilepsy

This study contributes to the literature by providing information regarding the utilization of ED and inpatient services among TSC patients, in addition to data regarding the associated costs of treatment. A study conducted in 2013 showed that among TSC patients, the experience of seizures was very strongly associated with hospitalization (Lennert et al., 2013); therefore, the inpatient admissions and associated expenditures were expected to be high among TSC patients with epilepsy.

Healthcare Utilization

Among the study population, the most common reasons for the initial ED visit were associated with epilepsy and other congenital anomalies. TSC patients with epilepsy were diagnosed with more comorbidities than those without epilepsy. Most ED visits were categorized as treat and release. Among those admitted as inpatients to the same hospital, the proportion of TSC patients with epilepsy was higher (72.6%) than the proportion of TSC patients without epilepsy (27.4%). The odds of hospital admission were nearly two-fold higher among those with epilepsy (OR and CI). This finding indicated that increased ED use among TSC patients with epilepsy may also lead to increased hospitalization. Contrary to expectations, however, individuals

with epilepsy had a shorter average length of stay (4.94 days) than those without epilepsy (6.76 days). This result is consistent with the findings from an earlier study by Lennert et al. (2013), which reported similar lengths of stay for neurologic-related hospitalization (6.03 days), compared with the length of stay among the control cohort for TSC-related hospitalization (6.80 days). This outcome could be attributed to the necessity of performing surgical procedures, comprehensive diagnostic testing, and other interventions, which often require more specialized care and the increased utilization of healthcare resources, leading to an increased length of stay. In addition, the length of stay among this population may also be attributed to unmeasured differences in the severity of comorbid conditions. Further research evaluating the clinical profiles and the drivers associated with prolonged inpatient stays among these patients improve our understand and expand the findings of this study.

ED and Inpatient Expenditures

This study also compared the mean total ED and inpatient charges between TSC patients with and without epilepsy. The overall mean annual expenditure for ED visits by TSC patients without epilepsy was slightly lower than that for patients with epilepsy. However, for an inpatient stay, TSC patients without epilepsy had higher total expenditures than TSC patients with epilepsy. Although individuals without epilepsy had higher average inpatient expenditures than those with epilepsy, the absence of epilepsy as a comorbidity did not increase the odds of being included in the highest expenditure group. The odds of high expenditures were increased among patients with pre-existing conditions, such as cancer and infectious diseases. Grade school (aged 6-9 years) TSC patients without epilepsy had higher annual expenditures than all other age groups. Nearly half (46.3%) of TSC patients with epilepsy were covered by public

health insurance (Medicare and Medicaid), compared with less than one-quarter (20.7%) of TSC patients without epilepsy. Among all patients, a higher proportion (67%) had Medicaid as the primary payer, suggesting that these patients were likely receiving disability compensation or were considered to have low incomes. This finding also suggested that public payers account for larger proportions of ED visits that lead to inpatient admissions among this population. This outcome is consistent with a study conducted by Wen et al. (2017), which reported that ED visits leading to inpatient admissions for more than 90% of pediatric epilepsy patients were covered by Medicaid. To our knowledge, no studies among the TSC-specific health services research literature has examined the demographic characteristics and costs among individuals on public insurance, especially Medicare and Medicaid, even though this may describe a high proportion of the TSC population.

Implications for Health Policy and Practice

Because TSC is frequently accompanied by comorbid health conditions, such as epilepsy and other chronic physical illnesses, a patient may be treated by numerous specialists. Although access to and the use of multiple healthcare providers is often perceived as good access to care, this situation can also be associated with many challenges, including additional burdens on caregivers and families. Policymakers should adopt and implement. Advocacy groups, such as the TSC Alliance, have developed information to help individuals with TSC identify specialty clinics and clinicians (TSC Centers of Excellence) and to actively engage with their physicians and other health providers (tsalliance.org, n.d.). These resources provide tools to help TSC patients and their families become active participants in their healthcare, by asking questions about the relationships between conditions, medication interactions and side effects, and facilitating communications between primary care physicians and specialists (tsalliance.org,

n.d.). Despite the availability of these resources, additional resources and programs remain necessary to improve patients' access to these specialized clinics. A study conducted by Rentz et al. (2015), reported that, although over 40 TSC Centers of Excellence have been designated in the United States, almost three-fourths of adult patients and half of pediatric patients in their study lived further than 100 miles away from a TSC clinic. The challenges of living with multiple health conditions also indicate the need for continuous health education for TSC patients and their caregivers, in addition to multidisciplinary medical team input (Northrup & Krueger, 2013). Patients often face significant difficulties in identifying the right medical expertise necessary to comprehensively and effectively manage their care. As TSC patients grow from childhood into adulthood, care coordination among various specialties can be critical during the transition from pediatric to adult healthcare services (Both et al., 2018). Care coordination can include the inclusion and evaluation of the viewpoints of the patients and their families, to gain insights into the difficulties associated with the care of these patients and the development of interventions that might improve the transition process to adult services. One possible solution for effective and efficient care coordination is the availability of facilities and clinics capable of treating both children and adult TSC patients, which would ensure efficient transitional healthcare and appropriate and continuous surveillance and disease management. State agencies can provide support for the development and delivery of health education programs and educational materials. For example, the Managing Epilepsy Well (MEW) network is a Centers for Disease Control and Prevention (CDC) research center program that aims to provide national leadership for the development, testing, and distribution of innovative self-management programs and training for epilepsy professionals, families, and individuals affected by epilepsy. Project UPLIFT, a program within the MEW network, provides self-management

programs that aim to empower people with epilepsy to manage and improve their mental health and quality of life. Similar programs can be expanded to include specialized and focus education and training for individuals with epilepsy coupled with rare genetic diseases, such as TSC. The results from this study can be used by policymakers and organizations to focus further investigations into the costs associated with care management and care delivery patterns among individuals with TSC.

Implications for Future Research

This analysis of health service utilization and expenditures among TSC patients with or without epilepsy highlights areas of potential future research. First, additional studies, using similar methods and other claims datasets, remain necessary to assess the generalizability of the study findings. The present study documented the increased odds of inpatient hospitalizations and emergency room use among TSC patients with epilepsy compared with those without epilepsy. Future studies should examine patterns of repeated hospital events, which could facilitate the identification of opportunities for the prevention of these events. Additional analyses of race/ethnicity differences, outpatient services, medication use, and ambulatory care among TSC patients, along with precise measurements of the various comorbidities, remain necessary to better understand the healthcare utilization and expenditures among this population. Research identifying barriers to medical and social service access can indicate specific targets for policy solutions and ensure equitable access to healthcare.

The findings from this dissertation study have raised additional questions regarding the factors that affect the lengths of hospital stays and annual expenditures. Future studies should include all diagnoses, treatments, and interventions in the claims data and should explore other comorbidity measures, especially given the unexpected result that TSC patients without epilepsy

experienced significantly longer lengths of stay and increased mean inpatient expenditures than patients with epilepsy, which may reflect unmeasured differences in the overall health status.

Limitations and Delimitations

To conduct this dissertation research, data were obtained from the largest, publicly available, all-payer database, for the period 2010-2014. All individuals diagnosed with TSC, either with or without epilepsy as a comorbidity, were included. Variations in demographic data were expected but were not controlled for during this analysis. Limitations include selection bias, which can occur because the outcomes being observed have already occurred at the time of selection. In addition, the use of retrospective, secondary data presents limitations, due to the lack of control in the selection of study variables and sampling and collection methods. Despite many advantages, the NEDS data is limited because it uses discharge-level, rather than a person-level, data. Therefore, multiple visits by individuals within the study population could not be distinguished.

This dissertation study is delimited to individuals with TSC associated with epilepsy. The decision to examine a specific data set and variables of interest also delimit the dissertation study. The NEDS data contains encounter-level records, not patient-level records; therefore, individual patients who visit the ED multiple times in one year may be present in the NEDS database multiple times. No uniform patient identifiers are available that would allow a patient-level analysis for the identification of individuals associated with more than one ED visit. The NEDs dataset did not include prescription medication use or associated expenditures or information regarding patient encounters with outpatient services and specialist clinics. Therefore, these results may not reflect the experiences of those who used outpatient services and specialist clinics, resulting in an incomplete assessment of healthcare utilization and

expenditures. Missing values from the obtained data can compromise the quality of estimates, resulting in bias and the inaccurate representation of inpatient and ED utilization patterns. Finally, racial/ethnic differences could not be accounted for in this study, due to the lack of information on race in the available data.

Conclusion

TSC inflicts a burden on society, imposing a significant burden on both individuals who have the condition and their families and caregivers. Despite the availability of FDA-approved medications for the treatment of TSC and its associated comorbidities, the results from this dissertation study suggested significant healthcare utilization and expenditures among this patient population. A better understanding of the utilization and cost patterns associated with TSC would facilitate the efficient allocation of resources while improving overall care for these patients.

TSC patients visit EDs for various reasons, beyond those associated with their primary condition or disease. ED visits among TSC patients with epilepsy were associated with increased hospitalization rates than those among TSC patients without epilepsy; however, for an inpatient stay, TSC patients without epilepsy experienced higher total expenditures than TSC patients with epilepsy. The increased expenditure among TSC patients without epilepsy may be attributable to the treatment of many underlying comorbidities. Access to medical and social services and the burden of healthcare utilization and expenditures among TSC patients have been understudied, and future research should examine the impacts of these critical factors (socioeconomic factors, care management, delivery, and cost patterns among individuals on public insurance, especially Medicare and Medicaid, versus private insurance) to develop solutions and strategies that can ensure the equitable access to healthcare.

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