

From THE DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

**EPIDEMIOLOGICAL STUDIES OF EPILEPSY:
INCIDENCE AND RISK FACTORS**

Cecilia Adelöw



**Karolinska
Institutet**

Stockholm 2011

All previously published papers were reproduced with permission from the publisher.
Bilder omslag: People, <http://www.flickr.com/photos/pocketpcian/3885629558> by
Tommy.Ian and RNS spike, <http://www.flickr.com/photos/thisparticulargreg/362937046>
by ThisparticularGreg

Published by Karolinska Institutet. Printed by Larserics Digital Print AB

© Cecilia Adelöw, 2011, ISBN 978-91-7457-407-4

In memory of my grandmother Inga

ABSTRACT

Epilepsy is one of the most common serious neurological disorders leading to significant consequences for the affected. Despite the wealth of epidemiological data, there are still many un-answered questions. The major challenges in epidemiological research relate to the fact that epilepsy is a heterogeneous condition which hampers the evaluation of subgroups of e.g. different seizure/epilepsy types and age groups.

The overall objective of the present research was to describe the incidence and some selected risk factors for unprovoked seizures/epilepsy in a large representative population based cohort. Four studies were carried out, using the Stockholm Incidence Registry of Epilepsy (SIRE), a large cohort of incident cases with unprovoked seizures and epilepsy. We first analysed the age- and sex-specific incidence of unprovoked seizures/epilepsy in Stockholm, Sweden. The age-adjusted incidence for unprovoked seizures/epilepsy was 40.4 for males, and 30.7 for females, and in the lower range of the incidence rates reported from Europe and the US. Although our incidence rates suggest a possible under-ascertainment in particular among the elderly, the distribution of cases by gender, seizure type and aetiology indicate that there is no major selection bias.

We then performed three separate case-control studies with cases from SIRE, the controls taken from the Population and Housing Census, and exposure defined as a hospital discharge diagnosis using ICD codes from the Swedish Hospital Discharge Registry. Case-control data were linked to the hospital discharge registry to identify a history of in-hospital care for the diagnoses chosen, from 1980 up to the year of the index seizure and also after the index seizure.

When analysing the risk of developing unprovoked seizures/epilepsy after hospitalization for stroke, diabetes and myocardial infarction, we could confirm, previously known increased risks of developing unprovoked seizures after intracerebral haemorrhage, odds ratio (OR) 7.2 (95% confidence interval (CI) 3.9-13.6) and cerebral infarction, OR 9.4 (95% CI 6.7-13.1), and a less pronounced risk increase after hospitalization for acute myocardial infarction, OR 1.7 (95% CI 1.4-2.8). The risk of developing unprovoked seizures/epilepsy was substantial even more than 7 years after the stroke.

Socioeconomic belonging was also studied as a potential risk factor for development of unprovoked seizures/epilepsy, and we did not find an association between socioeconomic class and risk of unprovoked seizures. Psychiatric disorders as risk factors for seizures/epilepsy was analysed, and increased rates were observed both predating, (OR 2.5 (95% CI 1.7-3.7) for depression, OR 2.7 (95% CI 1.4-5.3) for bipolar disorder, OR 2.3 (95% CI 1.5-3.5) for psychosis, and OR 2.6 (95% CI 1.7-4.1) for suicide attempt), as well as succeeding seizure onset.

We further analysed the risk, (OR, 95%CI), of developing unprovoked seizures/epilepsy after hospitalization for multiple sclerosis (MS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). The risk of unprovoked seizures was increased in patients with a hospital discharge diagnosis of MS, OR 3.5 (95% CI 1.5-8.1) and even more so for patients with SLE, OR 8.0 (95% CI 2.2-30.0), whereas RA was not associated with an increased risk, OR 1.2 (95% CI 0.5-2.9). We also found a comparatively high age and advanced disability at seizure onset as well as a long lag time from diagnosis of MS and SLE until seizure onset.

Keywords: seizure, epilepsy, incidence, risk factor, case-control, stroke, psychiatric disorder, multiple sclerosis

LIST OF PUBLICATIONS

This thesis is based on the following publications:

- I. **Adelöw C**, Åndell E, Åmark P, Andersson T, Hellebro E, Ahlbom A, Tomson T. Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE). *Epilepsia*. 2009;50(5):1094-1101
- II. **Adelöw C**, Andersson T, Ahlbom A, Tomson T. Prior hospitalization for stroke, diabetes, myocardial infarction, and subsequent risk of unprovoked seizures. *Epilepsia*. 2011;52(2):301-307
- III. **Adelöw C**, Andersson T, Ahlbom A, Tomson T. Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy. *Accepted for publication in Neurology*
- IV. **Adelöw C**, Andersson T, Ahlbom A, Tomson T. Unprovoked seizures in multiple sclerosis and systemic lupus erythematosus – A population-based case-control study. *Submitted*

The original articles (I and II) have been printed with permission from the publishers.

CONTENTS

1	BACKGROUND.....	7
1.1	INTRODUCTION.....	7
1.2	DEFINITIONS OF SEIZURES AND EPILEPSY	7
1.3	CLASSIFICATION OF SEIZURES AND EPILEPSY	8
1.3.1	Classification of seizures	9
1.3.2	Classification of epilepsies and epileptic syndromes.....	9
1.4	GUIDELINES FOR EPIDEMIOLOGICAL STUDIES OF EPILEPSY	10
1.5	DIAGNOSING SEIZURES AND EPILEPSY IN THE CLINICAL SETTING	10
1.6	INCIDENCE AND PREVALENCE OF EPILEPSY	11
1.7	RISKFACORS AND CAUSES	13
1.8	COMORBIDITIES.....	13
1.9	CONSEQUENCES OF EPILEPSY	14
1.10	TREATMENT	14
1.11	BACKGROUND TO PRESENT STUDIES.....	15
2	AIMS	16
3	SUBJECTS AND METHODS	17
3.1	SUBJECTS	17
3.1.1	The Stockholm Incidence Registry of Epilepsy (SIRE)	17
3.1.2	Definitions used in SIRE	18
3.1.3	Controls	19
3.2	METHODS.....	19
3.2.1	Seizure incidence and classification of seizures, epilepsies and aetiologies (PAPER I).....	19
3.2.2	Case-control studies with incidence seizure cases and exposure defined by hospital discharge diagnoses (PAPER II-IV)	19
3.2.3	Sources to define exposure	20
3.3	STATISTICAL ANALYSES	20
3.3.1	Paper I.....	20
3.3.2	Paper II-IV	20
3.3.3	Paper II	20
3.3.4	Paper III.....	21
3.3.5	Paper IV	21
3.4	ETHICAL CONSIDERATIONS.....	21
4	RESULTS.....	22
4.1	Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE) (PAPER I)	22
4.2	Prior hospitalization for stroke, diabetes, myocardial infarction, and subsequent risk of unprovoked seizures (PAPER II)	25
4.3	Hospitalization for psychiatric disorders before and after onset of unprovoked seizures (PAPER III)	27
4.4	Unprovoked seizures in multiple sclerosis and systemic lupus erythematosus - A population-based case-control study (PAPER IV).....	28

5	DISCUSSION	30
5.1	METHODOLOGICAL ASPECTS	30
5.1.1	Strengths of the studies	30
5.1.2	Limitations of the studies.....	30
5.2	RESULTS IN RELATION TO PREVIOUS RESEARCH.....	31
5.2.1	Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden (SIRE)	31
5.2.2	Prior hospitalization for stroke, diabetes, myocardial infarction and subsequent risk of unprovoked seizures	32
5.2.3	Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy	33
5.2.4	Unprovoked seizures in multiple sclerosis and systemic lupus erythematosus	
	34	
6	CONCLUSIONS	35
6.1	FUTURE PERSPECTIVES.....	35
7	ACKNOWLEDGEMENTS.....	36
8	REFERENCES.....	38

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AED	Antiepileptic drug
CI	Confidence interval
CNS	Central nervous system
CT	Computerized tomography
EEG	Electroencephalogram
GTCS	Generalized tonic clonic seizures
ICD	International classification of disease
ICH	Intracerebral haemorrhage
ILAE	International League Against Epilepsy
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
OR	Odds ratio
PAR	Population attributable risk
P	Prevalence
RA	Rheumatoid arthritis
RERI	Relative excess risk due to interaction
SAB	Subarachnoid haemorrhage
SES	Socioeconomic status
SIRE	Stockholm incidence registry of epilepsy
SLE	Systemic lupus erythematosus
SUDEP	Sudden unexpected death in epilepsy
TIA	Transient ischemic attack

1 BACKGROUND

1.1 INTRODUCTION

Epilepsy as one of the most common disorders of the brain has been known since the antiquity. In the ancient Grecian literature one can find the designation of “having seized” where seizure as a word derives from the Greek meaning “to take hold”. Hippocrates was the first known to place the origin of epilepsy in the brain and even to suggest treatment with drugs instead of religious rituals. He also introduced the concept of epilepsy as a paroxysmal brain disorder with altered behaviour in contrast to a specific disease.

Attempts to understand and explain epilepsy has during history been afflicted by religious and social explanations that have further burdened the patients. From John Hughlings Jackson’s concepts of cortical localization in the 1860s and William G. Lennox’s beliefs in the 1930s of interaction between genetic predisposition and environmental factors in the development of seizures, important progress has been made. Berger’s revolutionary invention of the electroencephalogram (EEG) in 1929 has been followed by advancements in neuroimaging and neurobiology that have changed our perception of epilepsy and also have had important implications for classification of seizure disorders.

It has been estimated that more than 10% in a population will once experience a seizure and about a third of these will go on to develop epilepsy [1]. Both in terms of prevalence and cumulative incidence, epilepsy is thus one of the most common serious neurological disorders, with the same burden of disease as lung cancer in men or breast cancer in women [2]. In addition to the threat of loss of control inherent to epilepsy, there is a risk of seizure-related injuries and psychosocial disability, an associated high rate of different comorbidities and a reduced life expectancy that add to the burden [3-6].

An assessment of the burden of disease rests on reliable epidemiological data, which also is essential for appropriate health care provision as well as for developing preventive measures. Epidemiological studies of epilepsy face specific problems related to the heterogeneity of the disorder as well as to difficulties in diagnosing epilepsy and in its classification. Definitions and classifications of the seizure disorders are therefore of fundamental importance.

1.2 DEFINITIONS OF SEIZURES AND EPILEPSY

There are definitions as well as classifications of seizures, epileptic syndromes and aetiologies and there are specific guidelines for epidemiological studies of epilepsy. As proposals for revision of these classifications have been put forward, both the former and the more recent classifications will be described.

Definitions of seizures

According to the present definition by the International League Against Epilepsy (ILAE) an *epileptic seizure* is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [7].

In epidemiological research as well as in the clinical setting a distinction has traditionally been made between unprovoked and provoked (*acute symptomatic*) seizures [8].

Unprovoked seizures are seizures occurring in the absence of a potential responsible condition or beyond the time interval estimated for acute symptomatic seizures.

Acute symptomatic seizures are seizures occurring at the time of a systemic insult or in close temporal association with a brain insult [8].

Examples of acute symptomatic seizures are epileptic seizures occurring within 1 week of stroke, traumatic brain injury, intracranial surgery, anoxic encephalopathy or during an active phase of multiple sclerosis. It also encompasses seizures during an active central nervous system infection, severe metabolic derangement, drugs or alcohol intoxication or withdrawal. In several aspects acute symptomatic seizures differ from unprovoked seizures. In acute symptomatic seizures there is an identifiable immediate cause of the seizure, often a dose – effect relationship and a different prognosis, e.g. not necessarily a tendency for recurrence of seizures [9]. The Commission on Epidemiology and Prognosis has developed criteria for each category of acute symptomatic seizures meant as guidelines for epidemiological research [8]. As acute symptomatic seizures are almost as common as epilepsy and the age distribution is similar [10-12], avoidance of misclassification of acute symptomatic seizures as unprovoked epileptic seizures may be difficult.

The concept of acute symptomatic seizures has however been questioned recently [13] and is not clearly considered in the 2005 ILAE definition of epilepsy [7] although the distinction between unprovoked and acute symptomatic seizures generally is considered important in epidemiological research.

Definitions of epilepsy

In the 1993 ILAE Commission report *epilepsy* was defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause [14]. In the more recent definition from 2005, *epilepsy* is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition [7].

This new definition requires the occurrence of at least one epileptic seizure and the presence of an enduring alteration in the brain increasing the likelihood of future seizures. This conceptual definition is intended for clinicians diagnosing epilepsy while most epidemiological studies, in need of clear operational criteria, still refer to the term epilepsy as a condition characterized by two or more unprovoked seizures.

1.3 CLASSIFICATION OF SEIZURES AND EPILEPSY

Traditionally epilepsy has been classified according to seizure type, presumed aetiology and when present, a constellation of clinical characteristics constituting an epileptic syndrome. The international classifications of seizures and epilepsies began with proposals by Gastaut in 1969 and the first internationally accepted classifications were published in 1970 [15, 16]. These classifications were updated for seizures in 1981 [17] and for syndromes in 1989 [18], although the changes were minor. These proposals have gained general acceptance and been widely used. The purpose of the classification was to provide common concepts to facilitate communication between clinicians and researchers. With improvements in neuroimaging and increased knowledge of the genetic contribution to some epileptic syndromes, perceptions of causes and

mechanisms of epilepsy have changed. To encompass these progresses the ILAE Commission on Classification and Terminology has very recently proposed revised terminology and concepts for organization of seizures and epilepsies [19]. This is still a proposal under discussion and has as yet not been approved or endorsed by the ILAE.

1.3.1 Classification of seizures

The seizure classification is based on seizure semiology and EEG findings.

In the 1981 classification focal seizures are those in which clinical and EEG changes indicate initial activation of a system of neurons limited to parts of one cerebral hemisphere. The focal seizures have been separated into simple and complex [17]. When consciousness is not impaired the seizure is classified as a *simple focal* (or partial) seizure and when impaired, as a *complex focal* (or partial) seizure. The classification addresses the possible evolution of a simple partial seizure into a complex partial or secondary generalized seizure. The *focal* (or partial) seizures are further subdivided in to those with; *motor signs*, *autonomic symptoms*, *somatosensory* or *special sensory symptoms* or *psychic symptoms*.

According to the same classification a seizure is classified as *generalized* if semiology and EEG findings indicate initial involvement of both hemispheres. Generalized seizures are subdivided in to: *absences*, *myoclonic-*, *tonic-clonic- (GTCS)*, *clonic-*, *tonic-* and *atonic- seizures*.

In the proposal for a new classification the concepts of focal and generalized seizures have been modified slightly. Seizures are labelled *focal* when the epileptic activity is originating within networks limited to one hemisphere, and seizures are considered *generalized* when the epileptic activity has arisen in or rapidly engaged bilaterally distributed networks [19]. The term *partial* seizures is replaced by *focal* to stress that it is not necessarily only a small area of epileptogenesis involved, and the term *complex partial* is abandoned in favour of a comment of whether consciousness is affected or not. The focal seizure may evolve to a bilateral convulsive seizure. Generalized seizures are further subdivided into: *absences*, *myoclonic-*, *GTCS*, *clonic-*, *tonic-* and *atonic seizures*. If there is insufficient evidence to characterize the seizure as focal, generalized or both it is labelled *unknown* [19].

1.3.2 Classification of epilepsies and epileptic syndromes

In the ILAE guideline from 1989 [18], the attempt was to classify epilepsy in terms of seizure type, EEG findings, anatomy, aetiology, and syndrome features. Just as the seizure classification, the epilepsies were first separated into epilepsies with *partial* (localization related epilepsies) or *generalized seizures* (generalized epilepsies). A second axis separated epilepsies by aetiology: known aetiology (*symptomatic* or secondary epilepsies) from the *idiopathic* (primary) and the *cryptogenic*. The ILAE task force defined an epileptic syndrome as a complex of signs and symptoms that define a unique epilepsy condition [18]. It is more than just a seizure type but not an epilepsy disease with a specific aetiology.

In the new proposal [19] the terms and concepts for the underlying cause of epilepsy have been revised. The terms *symptomatic*, *idiopathic* and *cryptogenic* have been replaced by the terms *structural-metabolic*, *genetic*, and *unknown*. This proposal has, however, been criticized for not

listing etiologies in any detail and controversies associated with assigning causation has been raised [20].

1.4 GUIDELINES FOR EPIDEMIOLOGICAL STUDIES OF EPILEPSY

Given the difficulties in diagnosing and classifying epilepsy detailed below, and that researchers in epidemiology generally have more limited data than the individual patient's clinician it is difficult to apply the more complicated classification schemes in epidemiological research. The ILAE Commission on Epidemiology and Prognosis has therefore issued specific guidelines for epidemiological studies on epilepsy [14, 21]. According to these guidelines *epilepsy* is defined as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate cause [14, 21].

As EEG is unavailable in many field surveys the classification of seizure type is predominantly based on clinical criteria, and seizure types are classified based on the 1981 ILAE system [17]. Thus, a seizure is considered *generalized* when there is no indication of a focal onset in symptomatology or anatomic localization. A seizure is considered *partial* when there is evidence of a clinical focal onset. The seizure is labelled *simple partial* when the ability to interact with the environment is maintained and *complex partial* when consciousness is impaired. The seizure is classified as *partial secondary generalized* when seizure activity propagates to generalization. When both generalized and partial seizures occur the category *multiple seizure types* is used. The term *unclassified seizures* is used when lack of information makes it impossible to classify the seizure.

1.5 DIAGNOSING SEIZURES AND EPILEPSY IN THE CLINICAL SETTING

As epileptic seizures are symptoms of diverse brain disorders, the diagnostic evaluation is variable and depending on the age and other characteristics of the patient. Despite availability of EEG and advances in imaging techniques and neurobiology, the history taking of seizure semiology from the patient and witnesses remains the basis for diagnosing epilepsy. EEG may, if epileptiform activity is found, give valuable information but cannot rule out the existence of epilepsy if the activity is normal. Likewise an abnormal EEG is not evidence of epilepsy. The value of EEG is primarily in giving clues to if a paroxysmal symptom or sign is epileptic in origin and to help in classifying the type of seizure or epileptic syndrome. EEG findings could thus provide useful information for prediction of prognosis and selection of treatment. Magnetic resonance imaging (MRI) has revolutionized the understanding of epilepsy as it allows a detailed examination of brain structure. MRI has proven superior to the computerized tomography (CT) in identifying presumed aetiological lesions in both adults and children with epilepsy [22, 23]. Long-term video-EEG monitoring can be very helpful in the differential diagnostic efforts in selected cases.

As epilepsy remains a clinical diagnosis primarily based on the clinician's evaluation of the history it is hardly surprising that misdiagnosis of epilepsy is fairly common. It has been reported that up to 20% of patients referred as refractory epilepsy cases to specialist centres in fact do not have epilepsy, but for instance syncope and non-epileptic attacks [24]. The lack of a specific laboratory confirmatory test for epilepsy complicates the clinical management as well as epidemiological research in epilepsy.

1.6 INCIDENCE AND PREVALENCE OF EPILEPSY

In epidemiology measures of disease occurrence are used in reference to a group of people. Incidence and prevalence are measures of disease occurrence where the incidence rate measures the frequency of disease onset, and the prevalence measures disease status [25]. The prevalence is a consequence of the incidence and the duration of disease, where the duration of disease is dependent on the rate of recovery and the rate of survival. Therefore the prevalence can be almost the same for a disease with high incidence and short duration (common cold) and a chronic disease with lower incidence and long duration (rheumatoid arthritis) [26]. Prevalence (P) is expressed as number of cases with epilepsy per 1,000 at a given time point, while incidence rates of epilepsy are usually expressed as the number of new onset cases per 100,000 patient years. While studies of point prevalence of epilepsy describe the burden of the disease in the population and are useful for determining health care needs, incidence studies are preferred when seeking information on risk factors, time trends and in evaluation of preventive and treatment measures undertaken.

Prevalence for epilepsy in Europe has been reported to be in the range of 4 to 15/1,000 [27-30]. Globally, higher rates have been reported in Africa [31-33] and South America [34] whereas the prevalence figures in Asia have been similar to those in Europe and the US [35, 36]. Although some of this variation can be explained by methodological differences e.g. in case ascertainment and inclusion criteria, these ranges might also reflect differences in aetiological factors and mortality.

Reported incidence rates of epilepsy in Europe and North America have ranged from 20 to 80 per 100,000 person years [10, 37-41] where case inclusion criteria and age-adjustment are important for a meaningful comparison between studies (Table 1). Two small community based studies from the county of Västerbotten, Sweden found a crude incidence rate of 34 to 56 /100,000 person years [38, 39]. The incidence rate in some developing countries has been reported to be two to three times the incidence in industrialized countries [42-45] whereas studies from some Asian countries have found incidence rates similar to those in Europe and North America [35, 46-48].

Table 1. Incidence of epilepsy in Europe and North America

Reference	Publication	Country/ Region	Number of cases	Incidence*			Comment
				Crude	Age- adjusted	Ages	
Joensen [49]	1986	Faroe Island	194	43	37	all ages	
Keränen [50]	1989	Finland	230	24		>15 years	
Loiseau et al. [10]	1990	France	494	44		all ages	SS
Forsgren et al. [39]	1990	Sweden	239	34		>17 years	SS
Sidenvall et al. [51]	1993	Sweden	73	61	58	<15 years	SS
Hauser et al. [37]	1993	US	275	48	51	all ages	
Olafsson et al. [52]	1996	Iceland	42	47	43	all ages	
Forsgren et al. [38]	1996	Sweden	160	56	58	>16 years	SS
Jallon et al.[53]	1997	Switzerland	176	46		all ages	SS
Annegers et al. [54]	1999	US	197	33	28	<65years	
MacDonald et al. [55]	2000	UK	69	46	79	all ages	
Öun et al. [56]	2003	Estonia	81	35		>19 years	
Olafsson et al. [40]	2005	Iceland	501	57	52	all ages	SS
Christensen et al. [57]	2007	Denmark	88616	69		all ages	
Casetta [58]	2011	Italy	188	57		<14 years	

SS=Single seizures included

* per 100,000 person years

In industrialized countries the incidence rate is high among the youngest children and low in the adult years to increase again in the elderly [10, 37, 38]. Since the 1990s it has been reported that the incidence rate among children is decreasing, while increasing among the oldest in the population [37, 58-60]. When temporal trends were analysed in a registry study from Finland, the incidence rate in the elderly exceeded that of children from the year 2000 and onwards [61]. Improved obstetric and neonatal care, vaccination programs, and decrease in head injuries and postnatal injuries, longer survival after stroke and an increased life expectancy were suggested as explanations for the declining rates among children and increasing rates in the elderly. This incidence pattern is different from what has been reported from some developing countries where the incidence is peaking in adulthood and no increase has been observed in old age [46, 62-64].

Most population based incidence studies report a slightly higher incidence among males compared to females [49, 50, 65]. This sex related difference in incidence is in most of the studies not statistically significant. A recent study from Finland found significantly higher incidence rates in eastern Finland compared to other parts of the country, suggesting significant differences also within a small country with a fairly homogeneous population [61].

1.7 RISKFACTORS AND CAUSES

A *risk factor* is a characteristic that is associated with a raised risk of a disease. All risk factors are not causal. Epilepsy is a heterogeneous condition with many different causes. In principle, any disease or lesion engaging the cerebral cortex can induce seizures and cause epilepsy. However, the mechanisms by which different lesions cause epileptic seizures are incompletely understood. Lesions found in one patient with epilepsy are also found in persons without seizures and we do not fully understand why similar lesions in an identical location do not cause seizures in all persons. The aetiology is evidently multifactorial. Genetic and other predisposing conditions may interact with environmental factors to influence the risk of developing seizures.

The risk factors for childhood epilepsy are different from those for epilepsy later in life [66]. The risk for epileptic seizures in childhood is increased by febrile seizures, head trauma [67], central nervous system (CNS) infection, mental retardation [68], cerebral palsy [37] and attention deficit hyperactivity disorder (ADHD) [69, 70].

There are several well established risk factors for epilepsy in adults. The risk of seizures after **head trauma** is related to the degree of brain injury and is highest shortly after the injury [71, 72]. In a retrospective cohort study from Rochester, Minnesota severe brain injury was associated with late seizures in 12% of adults [73]. In another cohort study from Rochester Minnesota, the risk of unprovoked seizures increased 16 times after encephalitis and four times after bacterial meningitis, where most of the seizures were seen within five years of the infection [74]. The prevalence of **brain tumours** among adults with newly diagnosed epilepsy is 12-16% in different studies [75-77]. **Stroke** has repeatedly been identified as the leading cause of epilepsy with adult onset [78, 79], and risk factors for stroke (hypertension, ischemic heart disease, diabetes and left ventricle hypertrophy), have also in the absence of a clinical stroke, been shown to increase the risk of seizures [80]. In Rochester, Minnesota the risk of seizures among patients with **Alzheimer's diseases (AD)** was increased tenfold [81]. Low **socioeconomic status (SES)** is associated with many established risk factors for epilepsy. Two studies, from UK and North America, found low SES to be associated with an increased risk of developing epilepsy [82, 83] while one Swedish study failed to confirm this association [84].

1.8 COMORBIDITIES

The term comorbidity implies the occurrence of one or several diseases/disorders apart from epilepsy. In principle three different scenarios can result in comorbidity between the seizure disorder and some other morbidity. First, epilepsy might either directly or indirectly e.g. through living conditions or antiepileptic drug (AED) treatment cause a medical condition, e.g. depression. Second some other disease may lead to epilepsy. In the third scenario a common factor or underlying pathology, (genetic or environmental), may independently lead both to epilepsy and some other morbidity e.g. depression. The terms *causal* comorbidity and *resultant* comorbidity have been introduced to describe the different types of inter-relationships between comorbidities [85].

The significant impact of epilepsy on the life of the affected person can be further burdened by comorbidity. In general comorbidity is associated with a decreased quality of life, a higher mortality [3, 86] and may require special consideration in the treatment of the comorbidity as well as of the epilepsy.

A cross-sectional population based study extracting data from the UK General Practice Research Database (1995-1998) estimated prevalence rates for selected conditions categorized by International classification of disease -9 (ICD-9) chapters in adults with epilepsy and compared them with adults without epilepsy [87]. Psychiatric conditions occurred twice as often and the risk of most somatic disorders was increased with the exception of musculoskeletal and connective tissue disorders in older adults.

Neurodegenerative conditions such as dementias (prevalence rate (PR) 6.3), AD (PR 8.0) and Parkinson's disease (PR 3.2) as well as cardio- and cerebrovascular disorders, fractures, pneumonia and diabetes occurred more frequently in people with epilepsy.

In a Canadian study using the National Population Health Survey an increased co-occurrence of ventricular ulcers, stroke, AD, chronic fatigue and migraine was shown [88] while the Epilepsy Comorbidity and Health (EPIC) survey in the United States [89] reported increased PRs for pain comorbidities (PR 1.4-2.0), asthma (PR 1.3) and movement disorders (PR 2.0).

Among children with epilepsy mental retardation and cerebral palsy are common as well as learning disabilities and cognitive dysfunction also in absence of other neurological deficits [90, 91].

1.9 CONSEQUENCES OF EPILEPSY

Epilepsy is a serious condition with significant consequences for the affected. Epilepsy can have a negative impact on a person's health status, socioeconomic and educational life [92-94].

Unemployment rates are generally higher for people with epilepsy than for the general population [95] and school achievements are less than in the general population even when persons with additional neurological handicap have been excluded [94]. Reports claim that also the frequency of marriage and fertility is decreased in patients with epilepsy compared to the general population [96, 97].

It is known that the mortality rate in epilepsy is two to three times higher than in the general population [98-102]. Causes of death can be unrelated to epilepsy, due to the underlying aetiology, to the treatment of epilepsy or more directly related to the occurrence of seizures. The seizure related mortality consists of cases that died in status epilepticus, accidents, in suicide or due to sudden unexpected death in epilepsy (SUDEP). Among patients with chronic uncontrolled epilepsy, SUDEP is the leading cause of death, while among new onset seizure patients the increased mortality is mainly due to the underlying causes of epilepsy [103-106]. In a multicentre cohort study the frequency of accidents was 21% among epilepsy cases and 13% among controls, were 25% of the accidents among patients with epilepsy were seizure related [107].

1.10 TREATMENT

Pharmacological treatment with AEDs is the dominating treatment modality and most people with epilepsy will be prescribed AEDs. The majority of those responds and become seizure free while on treatment [108]. Despite the availability of more than 20 AEDs, approximately one-third of individuals with epilepsy continue to have seizures while on medication. Although effective in preventing seizures in most cases, the currently available AEDs do not affect the long-term prognosis of the seizure disorder. Studies indicate that deferral of treatment does not alter the long term seizure prognosis in terms of remission [109, 110].

The AED therapy is typically maintained for several years and often for life. Therefore a decision to initiate treatment needs to be based on a risk-benefit analysis taking in to account the risk of further seizures, the severity of the seizures, their timing (during sleep or while awake), the risk of seizure-related morbidity and mortality as well as AED toxicity [111]. The choice of AEDs is based on efficacy for the individual's seizure type, but also on patient specific factors such as age, sex, childbearing potential, comorbidities, and concomitant medications.

Up to two-third of people with epilepsy achieve long-term seizure freedom or terminal remission [112, 113]. In a study from Rochester the probability of being in remission without medication 10 years after diagnosis was 36% in the idiopathic group, but less than 20% in the symptomatic group [114]. Predictors of a low chance of seizure remission are: documented aetiology, abnormal EEG, GTCS, a high seizure frequency after treatment onset and a syndrome pattern [115].

1.11 BACKGROUND TO PRESENT STUDIES

Despite the wealth of epidemiological data, there are still many un-answered questions. The major challenges in epidemiological research relate to the fact that epilepsy is a heterogeneous condition where the different types of seizures and epilepsies are most likely to vary in aetiology, comorbidity as well as in the consequences [116]. Large patient samples are therefore needed to analyse specific epilepsy sub-populations. Prospective population-based studies of incident cases are the ideal for assessment of the incidence of unprovoked seizures in the population, as well as for exploration of risk factors. However, such studies are uncommon. A limitation of most previous population-based incidence studies of epilepsy is the comparatively small number of included cases [117]. This is important considering the heterogeneity of epilepsy, and hampers the evaluation of subgroups of e.g. different seizure/epilepsy types and age groups.

The present studies were undertaken because of a relative lack of large scale population-based data on the incidence of unprovoked seizures, as well as of analytical studies addressing potential risk factors for development of unprovoked seizures.

2 AIMS

The overall aim of the present research was to describe the incidence and some selected risk factors for unprovoked seizures and epilepsy in a large population based cohort.

Specific aims of the projects were:

- To establish and evaluate a prospective surveillance system for new onset unprovoked seizures and epilepsy in Northern Stockholm, the Stockholm Incidence Registry of Epilepsy (SIRE).
- To study the age- and sex-specific incidence of unprovoked seizures/epilepsy in Stockholm, Sweden.
- To study the risk of developing unprovoked seizures/epilepsy after hospitalization for stroke, diabetes and myocardial infarction.
- To study socioeconomic belonging as a potential risk factor for development of unprovoked seizures/epilepsy.
- To study the risk of developing unprovoked seizures/epilepsy before and after hospitalization for a psychiatric disorder.
- To study the risk of developing unprovoked seizures/epilepsy after hospitalization for multiple sclerosis (MS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

3 SUBJECTS AND METHODS

3.1 SUBJECTS

The studies in this thesis are all based on seizure cases included in the Stockholm Incidence Registry of Epilepsy (SIRE), which covers the Northern part of Stockholm, an urban region with 998,500 inhabitants. Patients included in SIRE were used for the incidence study (paper I) and also constituted the cases in the case-control studies of risk factors (papers II-IV). The inclusion periods and number of subjects used in each study are given in table 2.

Table 2. Study populations in paper I-IV

			Cases			Controls	
	Study period	Ages	n	Median-age	Men/Women	n	Median-age
Paper I	Sep 2001-Aug 2004	all ages	1015	37	56/44	N/A	N/A
Paper II	Sep 2001-Aug 2006	>15 years	933	51	55/45	6039	46
Paper III	Sep 2000-Aug 2008	all ages	1885	33	55/45	15080	32
Paper IV	Sep 2000-Aug 2008	all ages	1885	33	55/45	15080	32

N/A= Not applicable

3.1.1 The Stockholm Incidence Registry of Epilepsy (SIRE)

In the year 2000 a registry was initiated for prospective identification of patients with newly diagnosed unprovoked seizures/epilepsy in Northern Stockholm, Sweden - the Stockholm Incidence Registry of Epilepsy (SIRE). The primary objective was to set up a population-based surveillance system based on data available in medical records that could function over time and thus permit longitudinal epidemiological studies in a large cohort of incident cases.

Multiple sources were used to identify potential incident cases of first unprovoked seizures and epilepsy among residents of Northern Stockholm. Three hospitals serve the inhabitants of this region, but only one has departments of neurology, neurosurgery, and paediatrics. The other two have outpatient clinics for adult neurological care. There is one central EEG-laboratory reading all EEGs from the region.

A network of reporting physicians and other health care professionals was established to identify potential cases. This consisted of all neurologists (private and public), paediatricians and geriatricians working in the area as well as nurses in nursing homes. Cases were also identified by review of all EEG requests to the central EEG-lab for investigation on suspicion of new onset seizures and screening of medical records of all new referrals to the neuro-oncology section of the Karolinska University Hospital. Additional methods to identify cases included review of medical records of all patients discharged from the department of Neurology or the

department of Paediatrics at the Karolinska University Hospital for the first time with an ICD code of G 40, G 41 or R 56.8, and review of paediatric emergency room records to evaluate possible cases not reported otherwise.

All potential cases were evaluated 6 months after the index seizure based on review of medical records by a panel, which consisted of a neurologist, neuro-paediatrician, and a resident in neurology, a resident in paediatrics, and the study coordinator, a trained nurse. Classification was made by consensus and the consistency in application of classification criteria over time was ascertained by re-review of all cases.

Patients with acute symptomatic seizures were not included. Each potential case was categorized as definite first unprovoked seizure or definite epilepsy (recurrent unprovoked seizures). Their seizures, epilepsies and etiological classes were classified according to the ILAE guidelines for epidemiological studies on epilepsy [14, 21].

3.1.2 Definitions used in SIRE

The following definitions are mainly based on the suggestions made by the ILAE Commission for studies on the epidemiology of the epilepsies [21] and were used in the classification of cases.

Epilepsy

A condition characterized by at least two unprovoked seizures occurring less than five years apart. Multiple seizures in a 24-h period were considered a single event as was an episode of status epilepticus [14].

Acute symptomatic seizures

Seizures occurring in close temporal relationship to an acute systemic, metabolic or toxic disturbance or in connection with an acute CNS insult [8].

Symptomatic epilepsy

Repeated unprovoked seizures caused by a known underlying condition leading to a static or slowly progressive CNS lesion.

Cryptogenic epilepsy

Repeated unprovoked seizures for which an underlying lesion is suspected, the exact nature of which has not been determined.

Idiopathic epilepsy

Certain epilepsies without a known underlying lesion, with a suspected genetic background and defined by a particular clinical characteristic, specific EEG findings and a typical age of onset.

Presumed aetiology

A condition preceding seizure onset, known to be an aetiological factor for epilepsy and compatible with the type of seizure/epilepsy of the case in question.

Index seizure

The seizure that prompted the patient to seek medical advice and that eventually led to their identification by the SIRE. This was not necessarily the patients' first seizure.

3.1.3 Controls

The controls in paper II-IV were randomly selected from the register of the Stockholm County Population and matched with the cases for gender and year of diagnosis. Each control had to be a resident in the catchment area at the time of diagnosis of the case.

3.2 METHODS

3.2.1 Seizure incidence and classification of seizures, epilepsies and aetiologies (PAPER I)

Based on information in medical records covering six months from the index seizure, the index seizure was classified according to the proposal of the ILAE [17]. This classification was applied based on three different levels of information. The first level relied only on the semiology of the index seizure as described in the available medical records. On the second level the index seizure was reclassified taking into account information on any unprovoked seizure preceding the index seizure and those occurring within 6 months after it. The classification of the index seizure on the third level took into account all available information in the medical records up to 6 months after the index seizure.

We classified the aetiology of our cases into the three broad categories: symptomatic, cryptogenic, and idiopathic [14, 21]. Symptomatic cases were subdivided into those with a static or progressive aetiology [21]. Among the symptomatic cases, those with neurological deficits from birth were identified separately.

All cases were assessed and classified on two levels for more specific types of risk factors and aetiologies. On the first level, data in the medical records indicating any condition that might be of relevance as risk factor was recorded. These were conditions present before the onset of the unprovoked seizure/epilepsy and that had been identified as potential risk factors in previous studies. On this level, individual cases could have more than one risk factor indicated. On the second level, these factors were evaluated with respect to the causal relationship to the seizures and the presumed aetiology in each case was established. This would be a condition preceding seizure onset, known to be an aetiological factor for epilepsy, and compatible with the type of seizures/epilepsy of the case in question.

Mental retardation and cerebral palsy were not considered as causes of epilepsy, but rather as manifestations of an earlier brain insult. The group: *other specified* was used for specific conditions with known association to epileptic seizures such as cerebrovascular malformations, tuberous sclerosis complex without known chromosomal defects, mesial temporal sclerosis, a history of a cerebral abscess or tuberculoma.

3.2.2 Case-control studies with incidence seizure cases and exposure defined by hospital discharge diagnoses (PAPER II-IV)

In these studies patients in SIRE were used as cases and controls were taken from the Population and Housing Census. Exposure was defined as a hospital discharge diagnosis using ICD codes from the Swedish Hospital Discharge Registry. Case-control data was linked to the hospital discharge registry to identify a history of in-hospital care for the diagnoses

chosen, from 1980 up to the year of the index seizure (paper II, IV) and also after the index seizure (paper III).

3.2.3 Sources to define exposure

The Hospital Discharge Registry is nationwide and provides ICD codes for all inpatient care in the country since 1969, and is considered to be virtually complete since 1980 [118].

From 1980–1986 diagnostic information was based on the Swedish version of the ICD-8 (WHO, 1967), from 1987–1996, ICD-9, (WHO, 1977), and from 1997 and onward, ICD-10 (WHO, 1994). The registry includes information on primary as well as additional discharge diagnoses, and all were used in study II-IV.

Information on socioeconomic classes was obtained for cases and controls through a record linkage to a registry maintained by Statistics Sweden with data from the Population and Housing Census (1960-1990) and expressed in 5 classes of employment and education (Class 1: Manual worker, 2: Salaried employee, 3: White collar worker, 4: Postgraduate education or self-employment, 5: Unemployed, unclassified) (paper II-IV).

3.3 STATISTICAL ANALYSES

3.3.1 Paper I

The number of incident cases of unprovoked seizures and epilepsy over the selected three year study period was assessed. Age and sex-specific incidence rates were calculated as well as age adjusted rates using the European Standard Population [119]. Calculation of the 95% confidence interval (CI) was done using the Poisson distribution [120].

Estimates of the number of person years were made with data from Statistics Sweden. We added the official populations on December the 31st of each year of the three years of case registration. The total number of person years was estimated at 2,863,763. Data were analysed using SAS 9.1.

3.3.2 Paper II-IV

We used logistic regression to calculate odds ratios (ORs) with 95% CI to assess the risk of developing unprovoked seizures/epilepsy after a first hospital admission for the diagnoses at study. For patients with more than one hospital admission, all the admissions were accounted for. The time in years from hospital admission for any of the diagnoses at study and seizure/epilepsy was calculated and expressed in ORs for different time intervals and separately for men, women, seizure type and presumed aetiological class. Data were analysed using SAS 9.2.

3.3.3 Paper II

In this paper we studied the discharge diagnoses diabetes, myocardial infarction, cerebral infarction, intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAB) and transient ischemic attack (TIA).

The potential interaction between two different discharge diagnoses was analysed, calculating the relative excess risk due to interaction (RERI) with cases and controls lacking these two diagnoses as the reference.

To assess the impact of the various risk factors, the population attributable risk percent (PAR %) was calculated [121, 122]. The PAR% is the percent of the incidence of a disease in the population (exposed and non-exposed) that is due to the exposure in question and that would be avoided if exposure was eliminated.

3.3.4 Paper III

In this paper we studied the discharge diagnoses depression, anxiety disorder, bipolar disorder, psychosis and suicide attempt. The time in years from a psychiatric discharge diagnosis or suicide attempt, until the index seizure, as well as from the seizure until a psychiatric discharge diagnosis or suicide attempt, was calculated. ORs were assessed for each different time interval and for single seizures and recurrent seizures separately. Cases without the specific discharge diagnosis constituted the reference in this calculation. The amount of overlap in between diagnoses was analysed.

3.3.5 Paper IV

In this paper we studied the discharge diagnoses MS, SLE and RA. The medical records for all identified cases with a hospital discharge diagnoses of MS or SLE were reviewed to obtain additional clinical data. The time in years from the MS and SLE diagnosis until index seizure was registered.

3.4 ETHICAL CONSIDERATIONS

Integrity and privacy issues are essential in any research on human subjects, and prior informed consent is often required from each individual research subject. This is, however, often not feasible in large scale register studies. In our view, the present project is an example of a situation where approaching each individual seizure case and control to obtain informed consent might generate more harm than protection. Many of the included cases might not be aware of their diagnosis and information on possible risk factors and consequences of their seizure disorder could cause undue anxiety. The Ethics Review Board at the Karolinska Institute, Stockholm, shared our position, granted approval of the studies and deemed that no individual informed consent was required. All data were anonymously analysed and without personal identification numbers traceable

4 RESULTS

4.1 NEWLY DIAGNOSED SINGLE UNPROVOKED SEIZURES AND EPILEPSY IN STOCKHOLM, SWEDEN: FIRST REPORT FROM THE STOCKHOLM INCIDENCE REGISTRY OF EPILEPSY (SIRE) (PAPER I)

Objective

To study the age- and sex-specific incidence of unprovoked seizures/epilepsy in Stockholm and report initial findings of patients with newly diagnosed single unprovoked seizures/epilepsy included in the Stockholm Incidence Registry of Epilepsy (SIRE).

Results

During the study 1015 patients (566 males) were included in SIRE as cases. Of these, 430 (42.4 %) had a first single unprovoked seizure, whereas 585 (57.6%) had recurrent seizures. For an additional 67 patients the available data did not allow a definitive classification of unprovoked seizures. Analysing single and recurrent unprovoked seizures together, the crude incidence was 35.4 /100, 000 person years (40.4 for males, and 30.7 for females), with the highest incidence the first year of life and among the elderly (Figure 1). The age adjusted incidence rate according to the European Standard Million [119] was 39.0 per 100, 000 person years. The incidence rates by age and sex are summarized in table 3. The age-adjusted incidence rates the three years of study were 32.6, 36.9 and 36.6 respectively. The proportion of GTCS, uncertain whether primary or secondary generalized, was reduced from 47.4% at the first level of seizure classification to 27.8% at the third level of classification. The cause of the unprovoked seizures was unknown in 62.4% (633/1015). In 85.2% of the patients an EEG was performed, in 77.4% a CT and in 20.9% a MRI, out of which 46.1%, 61.5% and 45.8% were normal. Generalized-onset seizures occurred in 9.9% of all cases while symptomatic static seizures accounted for 21.7% and symptomatic progressive seizures for 15.9%. Idiopathic seizures occurred in 7.9% whereas those with cryptogenic seizures constituted the largest group, 54.4%. A presumed aetiology was identified in 28.3% (108/382) of patients under 15 years, 37.4% (185/494) of those aged 15 to 69 years and in 64.0% (89/139) of those 70 years and older. Stroke was the most commonly identified aetiology followed by brain tumours. Neurological deficits from birth were noted in 10.3%.

Conclusions

We found the incidence of unprovoked seizures/epilepsy in Stockholm, for all age groups, to be in the lower range of what has been reported from Europe and the US. This indicates a possible under-ascertainment of cases and in particular among the elderly. The distribution among our cases by gender, seizure type, aetiological class and presumed aetiology are similar to previous studies.

Figure 1. Age and sex-specific incidence

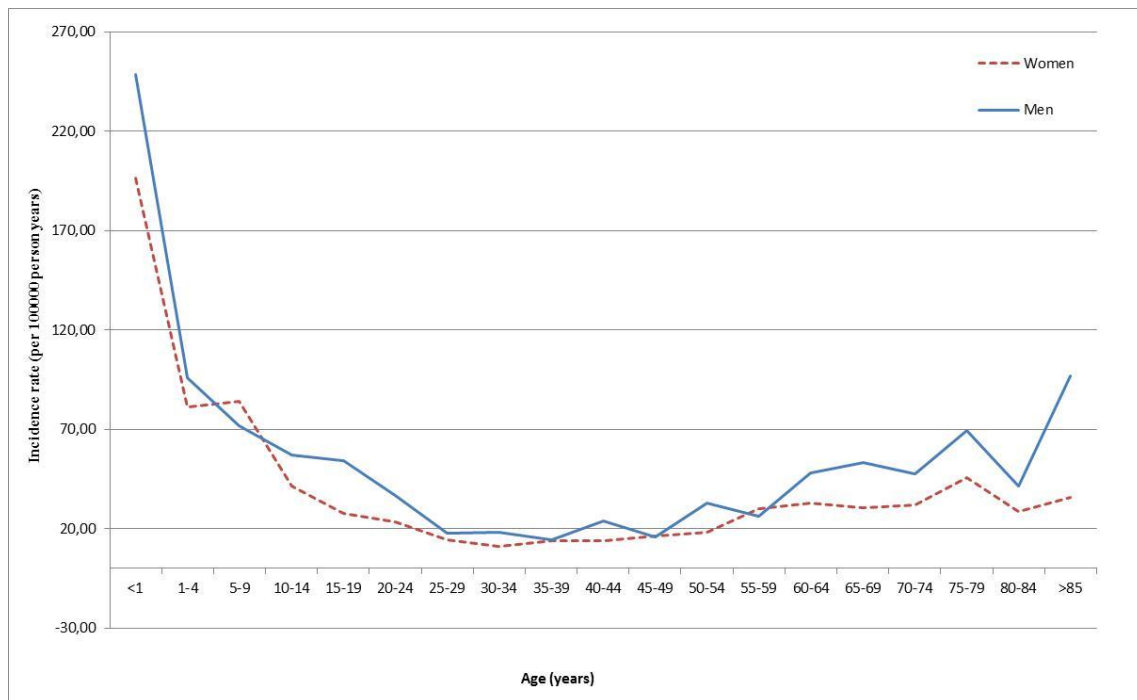


Table 3. Age- and sex specific incidence rates (per 100 000 person years) of unprovoked seizures/epilepsy in Northern Stockholm September 1st, 2001 through August 31st, 2004.

Age (years)	Total					Males			Females		
	Single unprovoked seizures	Epilepsy	Total number	Incidence rate	95% Confidence interval	Number	Incidence rate	95% Confidence interval	Number	Incidence rate	95% Confidence interval
<1	11	31	42	223,2	155,7 - 290,7	24,0	248,4	197,4 - 347,8	18,0	196,6	105,8 - 287,5
1-4	40	79	119	88,7	72,7 - 104,6	66,0	95,9	72,7 - 119,0	53,0	81,1	59,3 - 102,9
5-9	47	84	131	77,7	64,4 - 91,0	62	71,6	53,8 - 89,4	69	84,1	64,3 - 103,9
10-14	39	51	90	49,4	39,2 - 59,6	53	56,9	41,6 - 72,2	37	41,6	28,2 - 55,0
15-19	30	34	64	41,2	31,1 - 51,3	43	54,1	37,9 - 70,2	21	27,7	15,8 - 39,5
20-24	29	20	49	30,0	21,6 - 38,4	30	36,9	23,7 - 50,0	19	23,2	12,8 - 33,7
25-29	11	24	35	16,1	10,8 - 21,5	19	17,8	9,8 - 25,8	16	14,5	7,4 - 21,6
30-34	19	16	35	14,5	9,7 - 19,3	22	18,2	10,6 - 25,8	13	10,8	4,9 - 16,7
35-39	17	16	33	13,9	9,2 - 18,7	17	14,1	7,4 - 20,9	16	13,7	7,0 - 20,4
40-44	25	14	39	19,1	13,1 - 25,1	25	24,0	14,6 - 33,4	14	14,0	6,7 - 21,4
45-49	15	15	30	16,1	10,4 - 21,9	15	15,9	7,9 - 24,0	15	16,4	8,1 - 24,6
50-54	19	28	47	25,4	18,2 - 32,7	30	33,0	21,2 - 44,8	17	18,1	9,5 - 26,7
55-59	27	30	57	28,0	20,7 - 35,2	26	26,1	16,1 - 36,1	31	29,8	19,3 - 40,3
60-64	30	31	61	40,2	30,1 - 50,3	36	47,9	32,3 - 63,6	25	32,6	19,8 - 45,4
65-69	13	31	44	41,2	29,0 - 53,3	27	53,0	33,0 - 73,0	17	30,4	16,0 - 44,9
70-74	17	18	35	38,8	25,9 - 51,6	19	47,5	26,2 - 68,9	16	31,8	16,2 - 47,3
75-79	18	29	47	55,4	39,6 - 71,2	24	69,4	41,6 - 97,1	23	45,8	27,1 - 64,5
80-84	11	13	24	33,3	20,0 - 46,6	11	41,2	16,8 - 65,5	13	28,7	13,1 - 44,3
>85	12	21	33	53,1	35,0 - 71,2	17	96,9	50,8 - 142,9	16	35,9	18,3 - 53,5
Total	430	585	1015	35,4	33,3 - 37,6	566	40,4	37,1 - 43,7	449	30,7	27,9 - 33,5

4.2 PRIOR HOSPITALIZATION FOR STROKE, DIABETES, MYOCARDIAL INFARCTION, AND SUBSEQUENT RISK OF UNPROVOKED SEIZURES (PAPER II)

Objective

To study the risk of developing unprovoked seizures/epilepsy after hospitalization for stroke, diabetes and myocardial infarction, as well as socioeconomic belonging as a potential risk factor for development of unprovoked seizures/epilepsy.

Results

We found no association between socioeconomic class and risk of unprovoked seizures and there were no noteworthy differences in the ORs when analysed separately by sex or different age groups. Consequently, socioeconomic status was not considered a confounder and not included in further analyses.

The PAR% as well as the age-adjusted and gender-specific ORs for unprovoked seizures after hospitalization for diabetes, acute myocardial infarction, and cerebral infarction, ICH, SAB and TIA are given in table 4. The ORs were increased for all, but most prominently for the stroke diagnoses. The ORs as a function of time since hospitalization for diabetes, myocardial infarction, ICH and cerebral infarction are presented in table 5.

Table 4. Age-adjusted odds ratios (OR) with 95% Confidence interval (CI) for development of seizures/epilepsy after a first discharge diagnosis of diabetes, myocardial infarction (MI), subarachnoid haemorrhage (SAB), intracerebral haemorrhage (ICH), cerebral infarction (Cbl) or transient ischemic attack (TIA). Population attributable risk percent (PAR%) is the percent of the incidence of unprovoked seizures/epilepsy that is due to the diagnoses given below.

Diagnosis	Total			Women				Men			
	cases	controls	PAR%	cases	controls	OR	CI	cases	controls	OR	CI
Diabetes	46	123	1,9	13	54	1,2	0,6 2,3	33	69	2,5	1,6 3,9
MI	21	52	0,6	5	7	2,5	0,7 8,5	16	45	1,5	0,8 2,8
SAB	10	9	0,9	7	5	8,8	2,8 28,3	3	4	5,1	1,1 23,0
ICH	24	18	1,8	12	6	10,3	3,8 28,2	12	12	5,7	2,5 12,8
Cbl	117	69	8,8	52	29	9,2	5,6 15,1	65	40	9,6	6,2 15,0
TIA	28	35	1,3	15	14	4,5	2,1 9,5	13	21	2,4	1,1 5,0

Table 5. Age-adjusted odds ratios (ORs) with 95% confidence interval (CI) for timing in years of a diagnose of diabetes, myocardial infarction, intracerebral haemorrhage or cerebral infarction, relative to onset of seizures.

Diagnosis	Year	Cases	Controls	OR	CI		
Diabetes	Total	46	123	1,9	1,4	-	2,8
	Reference	887	5916	1	-	-	-
	<1	16	11	7,8	3,6	-	17,2
	1-3	12	31	1,8	0,9	-	3,7
	4-6	5	25	0,9	0,3	-	2,5
	7-9	4	17	1,1	0,3	-	3,2
	>9	9	39	1,4	0,7	-	3,0
Myocardial infarction	Total	21	52	1,7	1,0	-	2,9
	Reference	912	5987	1	-	-	-
	<1-3	0	0	-	-	-	-
	4-9	6	25	1,0	0,4	-	2,5
	>9	15	27	2,3	1,2	-	4,5
Intracerebral haemorrhage	Total	24	18	7,2	3,9	-	13,6
	Reference	909	6021	1	-	-	-
	<1	14	2	42,8	9,5	-	191,5
	1-3	6	7	4,9	1,6	-	15,0
	>4	4	9	2,0	0,6	-	6,7
Cerebral infarction	Total	117	69	9,4	6,7	-	13,1
	Reference	816	5970	1	-	-	-
	<1	58	5	62,7	24,9	-	158,3
	1-3	34	23	8,4	4,8	-	14,8
	4-6	8	16	2,2	0,9	-	5,4
	7-9	7	9	6,3	2,2	-	18,3
	>9	10	16	3,0	1,3	-	6,7

Where numbers are small the time intervals have been made broader.

Conclusions

We did not find an association between socioeconomic factors and risk of developing unprovoked seizures in adulthood. Taken together the studied diagnoses accounted for 15% of the incident cases of unprovoked seizures with cerebral infarction as the major contributor. The risk for unprovoked seizures and epilepsy after a cerebral infarction was highest the first year after the infarction and the risk remained substantial >7 years after the infarction diagnosis. We found a modest increase in risk for unprovoked seizures/epilepsy after a diagnosis of myocardial infarction and no indication of higher ORs after ICH than after cerebral infarction.

4.3 HOSPITALIZATION FOR PSYCHIATRIC DISORDERS BEFORE AND AFTER ONSET OF UNPROVOKED SEIZURES (PAPER III)

Objective

To study the risk of developing unprovoked seizures/epilepsy before and after hospitalization for a psychiatric disorder.

Results

Of the cases, 3.7% had either a discharge diagnosis of depression, psychosis, anxiety disorder or bipolar disorder. The corresponding figure for the controls was 1.4%. We found a 2-3-fold increased risk of developing unprovoked seizures after a hospital discharge diagnosis of all investigated psychiatric conditions including suicide attempt (Table 6), and a trend towards higher ORs in patients with cryptogenic/idiopathic aetiology compared to those with symptomatic aetiology. Among the suicide attempts almost 2/3 of both cases and controls were women. Significantly increased ORs were noted in relation to psychiatric disorders including suicide attempt more than 5 years before and more than 2 years after the index seizure, although the highest ORs were seen the years closest to the index seizure, and most distinctly for depression and psychosis (Table 7).

Table 6. Age-adjusted odds ratios (OR) with 95% Confidence interval (CI) for development of unprovoked, seizures/epilepsy after a first discharge diagnosis of depression, psychosis, bipolar disorder, anxiety disorder, suicide attempt or psychiatric disorders combined. Population attributable risk percent (PAR%) is the percent of the incidence of unprovoked seizures/epilepsy, that is due to a given diagnosis. Psychiatric disorders combined include all the above diagnoses except suicide attempt. Each patient can have more than one psychiatric diagnosis.

Diagnosis	Total				Men				Women			
	Cases	Controls	OR	CI	Cases	Controls	OR	CI	Cases	Controls	OR	CI
DS	36	105	2.5	1.7-3.7	17	38	3.5	1.9-6.2	19	67	2.1	1.2-3.5
PS	27	96	2.3	1.5-3.5	13	47	2.4	1.3-4.4	14	49	2.3	1.2-4.2
Bd	12	32	2.7	1.4-5.3	4	16	1.9	0.6-5.9	8	16	3.5	1.5-8.2
Ad	17	50	2.7	1.6-4.8	4	20	1.6	0.5-4.8	13	30	3.5	1.8-6.8
SA	28	95	2.6	1.7-4.1	9	34	2.4	1.1-5.0	19	61	2.8	1.7-4.8
PdC	69	206	2.7	2.0-3.6	30	91	2.7	1.8-4.2	39	115	2.8	1.9-4.1

DS=Depression, PS=Psychosis

Bd=Bipolar disorder

Ad=Anxiety disorder

SA=Suicide attempt

PdC=Psychiatric disorders combined

Table 7. Age-adjusted odds ratios (OR) with 95% Confidence interval (CI) for development of unprovoked seizures/epilepsy and time in years before and after a first diagnosis of depression, psychosis, suicide attempt or psychiatric disorders combined. The category psychiatric disorders combined includes the diagnoses: depression, psychosis, bipolar disorder and anxiety disorder.

Total epilepsy cases (n=1885)								
Time before/ after seizure diagnosis (years)	Psychiatric disorders combined		Depression		Psychosis		Suicide attempt	
	OR	CI	OR	CI	OR	CI	OR	CI
>5y before	2.6	1.8-3.7	2.2	1.3-3.7	2.1	1.3-3.4	2.2	1.3-3.8
2-5y before	2.7	1.4-5.2	1.6	0.6-4.2	2.5	0.7-8.9	3.8	1.6-9.4
<2y before	3.9	1.9-7.9	6.3	2.8-14.6	5.6	1.2-25.8	4.7	1.2-18.8
0-2y after	4.5	2.7-7.6	4.1	2.2-7.7	6.4	1.9-21.3	4.4	1.8-11.0
>2y after	1.9	1.3-3.0	1.7	1.0-2.8	2.5	1.0-6.3	2.2	1.1-4.4

Conclusions

The increased rate of psychiatric comorbidity predating and succeeding seizure onset indicates a bidirectional relationship where our results support the hypothesis of common pathogenic mechanisms for epilepsy and psychiatric disorders.

4.4 UNPROVOKED SEIZURES IN MULTIPLE SCLEROSIS AND SYSTEMIC LUPUS ERYTHEMATOSUS - A POPULATION-BASED CASE-CONTROL STUDY (PAPER IV)

Objective

To study the risk of developing unprovoked seizures/epilepsy after hospitalization for MS, SLE and RA.

Results

During the study period, eight of the 1885 seizure cases had been discharged from hospital with a diagnosis of MS, four with a diagnosis of SLE and six with a diagnosis of RA, the latter diagnosis chosen for comparison as an example of an immune-mediated disorder generally not affecting the CNS, (Table 8). The corresponding numbers for controls were 17, 5 and 33, respectively.

The age-adjusted ORs with 95% CI for unprovoked seizures was 3.5 (1.5-8.1) for a hospital discharge diagnosis of MS, 8.0 (2.2-30.0) for a diagnosis of SLE and 1.2 (CI 0.5-2.9) for a diagnosis of RA. Six of the eight patients with MS had no known risk factor for seizures other than MS. The index seizure was focal in all and in the form of status epilepticus in three of the eight patients with MS. Two of the four SLE patients had other neuropsychiatric symptoms than seizures. For the majority of cases more than 10 years elapsed from the MS and SLE diagnosis until seizure onset and at the time of the index seizure the majority of the MS patients had developed a secondary progressive disease or was substantially disabled by the disorder.

Table 8. Clinical features of MS and SLE patients identified in the incidence cohort of seizure cases.

Patient	Gender	Age at diagnosis of MS (y)	Age at first discharge diagnosis of MS	Age at onset of seizures (y)	Seizure type	Disease course MS*
1	f	23	30	45	Focal	moderate, PP
2	f	32	47	59	Focal	severe
3	f	55	64	65	Focal	mild
4	f	?	51	69	Focal	moderate/severe, PP
5	m	49	79	78	Focal	moderate, SP
6	f	30	31	31	Focal	SP
7	f	67	67	73	Focal	moderate/severe
8	m	?	55	73	Focal	severe

Patient	Gender	Age at diagnosis of SLE (y)	Age at first discharge diagnosis of SLE	Age at onset of seizures (y)	Seizure type	Disease course SLE	Other Neuropsychiatric Symptoms**
1	f	52	62	63	Focal	mild	0
2	m	39	46	55	Focal	mild	0
3	f	36	63	63	Focal	moderate	Cbl, MD, CIM, HA
4	f	18	50	59	Focal	mild	Cbl, MD

* PP=Primary-progressive, SP=Secondary-progressive

** Cbl=Cerebral infarction, MD=Mood disorder, CIM=Cognitive impairment, HA=Headache

Conclusions

This study supports and extends the findings of other authors suggesting that the risk of unprovoked seizures is increased in patients with MS and even more so for patients with SLE. We found high age, a long lag time from the MS and the SLE diagnosis until seizure onset, and advanced disability among the MS cases at seizure onset. This study lends further support to the role of inflammation in the pathogenesis of epilepsy.

5 DISCUSSION

5.1 METHODOLOGICAL ASPECTS

SIRE was established to create a large representative cohort of incident cases with unprovoked seizures and epilepsy that could be used for in-depth studies of risk factors for and consequences of epilepsy among other things. Paper I describes the methodology for this register and the age- and sex-specific incidence rates based on the study. The remaining three papers (II-IV) are utilising a similar methodology with SIRE data in case-control studies analysing selected risk factors for unprovoked seizures/epilepsy. As a well-known risk factor for seizures/epilepsy, we chose to study stroke together with disorders such as acute myocardial infarction and diabetes, the latter with a less well studied association to seizure disorders. Among the psychiatric disorders depression and suicide attempt, and their relationships to seizures/epilepsy, have been extensively studied and debated, but less data have been available on the temporal aspects of this association. The importance of inflammation and immunological factors for seizure development has been in focus the last years [123], and we therefor chose to study MS and SLE and the risk of developing unprovoked seizures [124-127].

5.1.1 Strengths of the studies

The strengths of these studies lie in the population-based approach and the use of a large incident cohort of cases with unprovoked seizures. The seizure diagnosis has been uniformly validated and all data have been assessed in a standardized manner following predefined operational criteria, applying the recommendations of the ILAE and excluding acute symptomatic seizures [14, 21]. The case-control studies used incident cases of unprovoked seizures from SIRE and controls from the general population of the same geographical region. Major strengths of the case-control studies were the use of a nation-wide independent registry to determine exposure (hospital discharge diagnoses). This gave us the possibility to compare the risk of developing seizures in exposed and unexposed and provide risk estimates that are likely to be valid for the general population. We also had information on the index date of the seizure, and data on exposure recorded in routine hospital care and independent of the seizure onset, thus avoiding recall bias. A further advantage was the possibility to survey the temporal association between the exposure and seizure onset for a timespan of more than twenty years. Using population data we were able to analyse socioeconomic status as a potential confounder, as well as a risk factor for unprovoked seizures.

5.1.2 Limitations of the studies

While our methodology has enabled us to register a large number of incident cases, there are also limitations with the design of SIRE. The registry is based entirely on data included in medical records, and their quality set the limit. As SIRE does not include a standardized work-up the availability of EEG and neuroimaging depended on if the patient's physician initiated such investigations. The six months limit after the index seizure also complicates classification as many cases cannot be readily classified into an epilepsy syndrome group at that stage. Together with our application of strict criteria for classification all these factors contribute to a relatively large proportion of patients with cryptogenic or unclassified seizures.

It is likely that there is an under-ascertainment of cases in SIRE. This is most obvious for the oldest in residential care that may be less likely to seek hospital care for a new onset seizure. Although probably rare, patients may seek medical advice for their seizures in regions outside Northern Stockholm and if so, are not identified by the registry. Failure to report a potential case or to identify symptoms as possible seizures could also contribute as well as unwillingness or forgetfulness of physicians in reporting cases. To reduce this risk, personal contact and repeated information was given to physicians, nurses and secretaries taking part in the reporting process. Case-ascertainment does not seem to change over times as the incidence rates were fairly constant over the three years under study.

In the case-control studies exposure was defined by a hospital discharge diagnosis, and patients not hospitalized for the diagnosis in question will thus not be included in the study. For selected diagnoses this may add to the under-ascertainment as well as introduce a possible selection bias towards more severe forms of diseases. Uncomplicated cases with diabetes will probably not be hospitalized. The first hospital discharge diagnosis of diabetes will in many cases not represent the onset of the disease and the onset often precedes the first discharge diagnosis. For these reasons we believe that our data on diabetes should be interpreted with particular caution.

Many patients with depression and not least anxiety disorders are diagnosed and managed as out-patients or not diagnosed at all. Our data on psychiatric disorders thus likely represent the more severe forms that require hospitalization. The high proportion of patients with more than one psychiatric discharge diagnosis supports this notion, where diagnoses such as anxiety disorder and depression more often in combination with a more severe psychopathology may call for hospitalization. It cannot be ruled out that hospitalization for a psychiatric disorder after seizure onset is influenced by the seizure diagnosis. It is also possible that many MS and SLE patients had disease onset before the first hospitalization for their condition, and that we thus underestimate the lag time to seizure onset. None of these limitations should however affect the case control comparison and the point estimate of the ORs.

A further limitation is that we rely on the ICD codes from the hospital discharge registry. With the exception of schizophrenia, [128, 129] the ICD codes that we have used from the Swedish Hospital Discharge Registry have not been formally validated although we have reason to believe that the codes we have selected have a high accuracy in the hospital discharge registry [130, 131].

The observation period of more than 20 years infers that virtually all cases with clinically significant disease should have been hospitalized at least once and thus included in the study and, there is no reason to expect a difference between cases and controls in this respect.

5.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

5.2.1 Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden (SIRE)

We found an age-adjusted incidence for unprovoked seizures/epilepsy of 35.4 /100, 000 person years, and the highest incidence in the first year of life and among the elderly. These figures are in the lower range of the incidence rates of 24 to 69/100, 000 reported from Europe and the US [10, 37, 38, 40, 49, 50, 53, 57]. In accordance with most previous population based studies [37, 49, 50, 52, 53, 56, 57] the incidence was in general higher among males than females, especially above

60 years of age, while at 5-9 years of age the highest incidence was observed among girls. The incidence rates in our study seemed to be lower in all age groups compared to most previous studies [37, 38, 49, 51-55, 62, 64, 132-136] although this difference was most pronounced among the elderly. However, the distribution among our cases by gender, seizure type, and aetiology are in keeping with previous studies, indicating that there is no pronounced selection bias in these respects [10, 37-39, 53, 54, 56, 133, 134, 137].

Many previous studies have failed to account for detailed operational criteria for the seizure classification, although in general referring to the ILAE classification [138]. The 27.8% considered to have unclassified seizures in our study is higher than in most other reports [134, 139, 140]. This can be explained by our dependence on medical records, the short follow-up, and the comparatively low proportion of neuroimaging, but also by our application of strict criteria for classification. The presumed aetiologies among our cases were similar to those reported in other population based studies of epilepsy [37, 40, 52, 53, 133]. Stroke was the most common cause followed by brain tumours. We found slightly fewer patients with stroke, 11.3% of the cases to compare with 14-20% in other studies from the US and Europe [38, 52, 56, 134, 139], and 2.2% of presumed causes with dementia, to compare with 3.5-14.8% [37, 38, 40, 53]. A higher proportion with dementia and stroke could be expected with a more efficient case ascertainment among the elderly, but our strict criteria for presumed aetiology versus risk factors could also contribute.

5.2.2 Prior hospitalization for stroke, diabetes, myocardial infarction and subsequent risk of unprovoked seizures

We found an increased risk for development of seizures after all types of stroke, for both sexes, and in particular the first year after hospitalization. Previous studies have shown an increased risk for development of seizures after ischemic and haemorrhagic stroke, including SAB in some series. This risk has in most previous studies been higher after ICH than after cerebral infarction [141-143], while we found no trend in that direction. Of the cases with cerebral infarction, 22% had more than one hospital admission for that specific diagnosis, confirming a high recurrence rate and with that presumably an increased risk for additional cortical damage and subsequent seizures. Age did not appear to influence the risk of seizure after stroke in our study in keeping with previous findings [144, 145]. Also in agreement with previous studies [146-149], the highest risk of seizures was seen during the first year after stroke, irrespective of the type of stroke. Cohort studies such as the Oxfordshire community stroke project [148] and the population-based study from Rochester [147] both showed a significant excess risk the first year after stroke. Cumulative rates of developing late seizures after cerebral infarction of 5–7.4% by year 5 [147] have been found, whereas the prevalence of post stroke epilepsy 7–8 years after an ischemic stroke was 3.1% in the Akershus Stroke Study [150].

Our study shows that the risk of seizures is substantially increased well beyond 7–10 years post stroke. Calculating PAR% we could show that prior hospitalization for stroke accounts for 12.8% of patients with new-onset unprovoked seizures/epilepsy in the adult population where cerebral infarction was the major contributor.

Few studies have analysed the association between myocardial infarction and seizures. The modest increase in OR for development of seizures after a discharge diagnosis of myocardial infarction did not follow the pattern of stroke with an excess risk seen the first year after the

diagnosis, but was highest >9 years after the myocardial infarction. There are limited data on diabetes as a risk factor for epilepsy. A previous smaller Swedish case-referent study reported an OR for the risk of developing unprovoked seizures of 2.7 for diabetes ($p = 0.31$) [84]. We included this diagnosis for the possibility of an interaction with the other risk factors in our study, an interaction which was not supported by our results.

We found no association between socioeconomic class and risk of unprovoked seizures. Although indices of low socioeconomic status are associated with many established risk factors for epilepsy, previous studies of the association are conflicting [82, 84]. Poor socioeconomic status was a risk factor for epilepsy in studies from England [82], Iceland [83], and the United States [151], whereas a previous smaller Swedish study [84], in agreement with ours, did not find an association between socioeconomic factors and risk of developing unprovoked seizures in adulthood. The comparatively small differences in socioeconomic standard in Sweden might contribute to our observations.

5.2.3 Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy

Little is known about the interaction between bipolar disorder and epilepsy [152]. The association between epilepsy and depression has been studied more extensively. The time sequence between onset of seizures and psychiatric conditions has, however, rarely been assessed before. Our findings of an increased frequency of depression preceding the seizure disorder among cases compared to controls are in accordance with the results of two previous population based studies [84, 153]. Hence, a case-control study from Iceland comprising 324 cases and 647 controls, found that people with incident unprovoked seizures were 1.7-fold more likely to have a history of major depression [153]. A much smaller Swedish study reported a 7-fold increased risk of developing unprovoked seizures with a prior history of depression [84]. Although the study from Iceland has the advantage of a rigorous validation and classification of the depression diagnosis using DSM-IV criteria, both previous studies obtained their information through interviews after seizure onset with inherent risks of recall bias [84, 153]. The association between epilepsy, suicide and suicide attempt has attracted much attention [154, 155]. A Finnish population based register study found that 1.3% ($n=25$) of suicide victims had a prior history of epilepsy [156], while larger register based studies from Denmark and Iceland have shown a 3-5-fold increased risk of suicide among epilepsy patients [153, 157]. We found an OR of 2.6 for unprovoked seizures after suicide attempt, based on 28 cases (1.5 %) and 95 controls (0.6%), and a significantly increased risk (OR 2.8, CI 1.6-4.8) of suicide attempt also after the index seizure. Our observed trends towards greater risks for patients with cryptogenic/idiopathic seizures versus seizures with a known underlying aetiology are in line with Hesdorffer's data [153]. The treatment of epilepsy might increase the risk of psychiatric conditions as some AEDs can have adverse effects on mood and behaviour [158-160]. Likewise, some antidepressants and antipsychotics might increase or even decrease the risk of seizures [161, 162]. Unfortunately, we did not have access to data on drug prescriptions to cases or controls and could not analyse the possible contribution of prescribed drugs on the risk of developing seizures.

Much of the discussion on psychiatric comorbidities has revolved around the questions of whether these are causes or consequences of the seizure disorder, if both alternatives may be operating, or if the comorbidities are causes common for epilepsy and psychiatric conditions [163-165]. The temporal association between seizures and psychiatric disorders found in our data is pointing towards the latter. Structural and functional abnormalities in frontal and temporal lobes and abnormal secretion of neurotransmitters such as serotonin have been suggested as potential explanations [166-168].

5.2.4 Unprovoked seizures in multiple sclerosis and systemic lupus erythematosus

We are not aware of any previous population-based case-control study assessing the risk of developing unprovoked seizures or epilepsy in patients with SLE. Two retrospective studies based on SLE cohorts reported a prevalence of seizures of 11-13 % [169, 170] were the frequency of seizure recurrence was 12-43 % [171, 172].

The age-adjusted OR (95% CI) for unprovoked seizures was 3.5 (1.5-8.1) for a hospital discharge diagnosis of MS and 8.0 (2.2-30.0) for a diagnosis of SLE. Our estimate of the risk of developing unprovoked seizures in MS is very similar to the standardized incidence ratio of 3.0 reported from a population-based study in Iceland [173] although the risk increase in that study was not significant due to the small sample size. Methodological differences hamper a meaningful comparison with previous studies that report prevalence rates of seizures/epilepsy ranging from 0.5% to 10.8% in different mainly hospital-based MS cohorts [124, 125, 174, 175].

In comparison with some other studies we noted a high mean age at seizure onset both for the MS [175-177] and the SLE cases [170, 172, 178]. One explanation for this discrepancy could be that previous studies included acute symptomatic seizures. In line with our findings others have observed that seizures are unusual in the primary progressive course of MS [179, 180].

6 CONCLUSIONS

We have established a system for prospective identification and follow-up of patients with newly diagnosed unprovoked seizures in Northern Stockholm, SIRE. In the present thesis, we have used this registry to analyse the age and sex-specific incidence of single unprovoked seizures and epilepsy and to perform case-control studies of selected known and potential risk factors for epilepsy.

- The age-adjusted incidence for unprovoked seizures/epilepsy was in the lower range of the incidence rates reported from Europe and the US. Rates were highest in children less than 1 year and in the 75-79 years old. The distribution of cases by gender, seizure type and aetiology indicate that there is no major selection bias except for a likely under-ascertainment among the elderly. Incidence rates were similar across the three years study period, suggesting sustainability in the ascertainment of cases.
- We could confirm, and quantify, previously known increased risks of developing unprovoked seizures after a stroke, with similar ORs after cerebral infarction and ICH. The risk was substantial even more than 7 years after the stroke. We could also demonstrate a less pronounced risk increase after hospitalization for acute myocardial infarction.
- We did not find an association between socioeconomic class and risk of unprovoked seizures/epilepsy.
- We observed increased rates of hospital discharge diagnoses for psychiatric disorders (depression, bipolar disorder, psychosis) and suicide attempt both predating and succeeding seizure onset indicating a bidirectional relationship between psychiatric disorders and seizures/epilepsy.
- The risk of unprovoked seizures/epilepsy was increased in patients with a hospital discharge diagnosis of MS and even more so for patients with SLE, whereas RA was not associated with an increased risk. We found a long lag time from diagnosis of MS and SLE until seizure onset and a comparatively high age and advanced disability at seizure onset.

6.1 FUTURE PERSPECTIVES

The identification and inclusion of cases in SIRE is continuing with more than 2000 included incident seizure cases at present date. The methodology using the Hospital Discharge Registry with exposure defined as ICD-diagnoses can be used for any other exposure and is well suited for studies of injuries and accidents as an example. The registry for Prescription, set up in year 2005, also offer new opportunities of studying treatment patterns for cases included in SIRE.

7 ACKNOWLEDGEMENTS

I wish to thank everyone who has contributed to this thesis and especially:

Professor **Torbjörn Tomson** my supervisor. I cannot think of a better teacher in the world of science! Thank you for your time, your tireless enthusiasm, intellectual brilliance and attention to both structure and details.

Professor **Anders Ahlbom** my co-supervisor for valuable advice, pleasant cooperation and for providing me a stimulating environment at IMM, KI

Tomas Andersson for patience, endless help with the database and statistical expertise.

The “epilepsy research group”:

Eva Hellebro for all support given and for being a fantastic mother of the SIRE with impressive order and structure.

Per Åhmark for good discussions and clinical knowledge of childhood epilepsies.

Eva Åndell for sharing problem-solving discussions of research and life.

Doc. **Lars-Olof Ronnevi**, head of the Department of Neurology, Karolinska University Hospital for giving me the opportunity to combine clinical work with a research education.

Doc. **Magnus Andersson**, div. head of the Department of Neurology Karolinska University Hospital, Solna, for giving all the time for research despite the efforts of staffing the clinic.

Åsa Vilhelmsson for invaluable help with administrative and practical issues

All my hard working **colleagues at the Department of Neurology**, KS, Solna, for being supportive and god friends.

The **colleagues at IMM**, for practical assistance and encouragement, and for always making me feel as part of the IMM institution although I officially never was.

Annika Gustavsson for assistance with ordering of data and setup of the database.

Maria Elb for all the help with administrative issues.

Jaan and **Eva** at the Neurology Clinic in Vällingby - thank you for encouragement and flexibility!

My dear friend **Alexandra** for constructive criticism of the manuscript.

My extended **family** and all dear **friends** inside and outside the medical world – Thank you!

My parents **Ulla** and **Björn** for never ending love, a positive attitude towards everything I do, and for all the practical support with the boys among many other things.

Sweet sister **Catharina** and brother **Johan** with a heart of gold - thank you for always being there!

Leif and my sons: **Emil**, **John** and **Nils** for all your love and patience.

This research project was supported by grants from GlaxoSmithKline, AFA research fund and the Stockholm County Council (ALF).

8 REFERENCES

1. Hesdorffer, D.C., et al., *Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota*. Neurology, 2011. **76**(1): p. 23-7.
2. Kale, R., *Bringing epilepsy out of the shadows*. Bmj, 1997. **315**(7099): p. 2-3.
3. Kessler, R.C., et al., *Accounting for comorbidity in assessing the burden of epilepsy among US adults: results from the National Comorbidity Survey Replication (NCS-R)*. Mol Psychiatry, 2011.
4. Cardarelli, W.J. and B.J. Smith, *The burden of epilepsy to patients and payers*. Am J Manag Care, 2010. **16**(12 Suppl): p. S331-6.
5. Tellez-Zenteno, J.F., R. Nguyen, and L. Hernandez-Ronquillo, *Injuries, accidents and mortality in epilepsy: a review of its prevalence risk factors and prevention*. Rev Invest Clin, 2010. **62**(5): p. 466-79.
6. Tomson, T., et al., *Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention*. Epilepsy Res, 2004. **60**(1): p. 1-16.
7. Fisher, R.S., et al., *Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)*. Epilepsia, 2005. **46**(4): p. 470-2.
8. Beghi, E., et al., *Recommendation for a definition of acute symptomatic seizure*. Epilepsia, 2010. **51**(4): p. 671-5.
9. Hesdorffer, D.C., et al., *Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure*. Epilepsia, 2009. **50**(5): p. 1102-8.
10. Loiseau, J., et al., *A survey of epileptic disorders in southwest France: seizures in elderly patients*. Ann Neurol, 1990. **27**(3): p. 232-7.
11. Hauser, W.A., J.F. Annegers, and L.T. Kurland, *Prevalence of epilepsy in Rochester, Minnesota: 1940-1980*. Epilepsia, 1991. **32**(4): p. 429-45.
12. Annegers, J.F., et al., *Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984*. Epilepsia, 1995. **36**(4): p. 327-33.
13. Shorvon, S. and R. Guerrini, *Acute symptomatic seizures--should we retain the term?* Epilepsia, 2010. **51**(4): p. 722-3.
14. *Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy*. Epilepsia, 1993. **34**(4): p. 592-6.
15. Gastaut, H., *Clinical and electroencephalographical classification of epileptic seizures*. Epilepsia, 1970. **11**(1): p. 102-13.
16. Merlis, J.K., *Proposal for an international classification of the epilepsies*. Epilepsia, 1970. **11**(1): p. 114-9.
17. *Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy*. Epilepsia, 1981. **22**(4): p. 489-501.
18. *Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy*. Epilepsia, 1989. **30**(4): p. 389-99.
19. Berg, A.T., et al., *Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009*. Epilepsia, 2010. **51**(4): p. 676-85.
20. Shorvon, S.D., *The etiologic classification of epilepsy*. Epilepsia, 2011. **52**(6): p. 1052-7.
21. *ILAE Commission Report. The epidemiology of the epilepsies: future directions. International League Against Epilepsy*. Epilepsia, 1997. **38**(5): p. 614-8.

22. Theodore, W.H., et al., *Pathology of temporal lobe foci: correlation with CT, MRI, and PET*. Neurology, 1990. **40**(5): p. 797-803.
23. Kuzniecky, R., et al., *Magnetic resonance imaging in childhood intractable partial epilepsies: pathologic correlations*. Neurology, 1993. **43**(4): p. 681-7.
24. Leach, J.P., et al., *Epilepsy in the UK: misdiagnosis, mistreatment, and undertreatment? The Wrexham area epilepsy project*. Seizure, 2005. **14**(7): p. 514-20.
25. Rothman, K., *Epidemiology An introduction*. 2002, New York: Oxford University Press, Inc.
26. Ahlbom A, A.L., Alfvén T, Bennet A, *Grunderna i Epidemiologi*. Third ed. 2006: Författarna och Studentlitteratur.
27. Forsgren, L., et al., *The epidemiology of epilepsy in Europe - a systematic review*. Eur J Neurol, 2005. **12**(4): p. 245-53.
28. Josipovic-Jelic, Z., et al., *Prevalence and socioeconomic aspects of epilepsy in the Croatian county of Sibenik-Knin: community-based survey*. Epilepsy Behav, 2011. **20**(4): p. 686-90.
29. Linehan, C., et al., *Examining the prevalence of epilepsy and delivery of epilepsy care in Ireland*. Epilepsia, 2010. **51**(5): p. 845-52.
30. Schiariti, V., et al., *Period prevalence of epilepsy in children in BC: a population-based study*. Can J Neurol Sci, 2009. **36**(1): p. 36-41.
31. Preux, P.M. and M. Druet-Cabanac, *Epidemiology and aetiology of epilepsy in sub-Saharan Africa*. Lancet Neurol, 2005. **4**(1): p. 21-31.
32. Yemadje, L.P., et al., *Understanding the differences in prevalence of epilepsy in tropical regions*. Epilepsia, 2011. **52**(8): p. 1376-81.
33. Forsgren, L., *Estimations of the prevalence of epilepsy in sub-Saharan Africa*. Lancet Neurol, 2008. **7**(1): p. 21-2.
34. Placencia, M., et al., *Epileptic seizures in an Andean region of Ecuador. Incidence and prevalence and regional variation*. Brain, 1992. **115** (Pt 3): p. 771-82.
35. Mac, T.L., et al., *Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review*. Lancet Neurol, 2007. **6**(6): p. 533-43.
36. Tuan, N.A., et al., *The prevalence of epilepsy in a rural district of Vietnam: a population-based study from the EPIBAVI project*. Epilepsia, 2008. **49**(9): p. 1634-7.
37. Hauser WA, A.J., Kurland LT, *Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984*. Epilepsia, 1993. **34**: p. 453-468.
38. Forsgren L, B.G., Eriksson S et al., *Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study*. Epilepsia, 1996. **37**: p. 224-229.
39. Forsgren, L., *Prospective incidence study and clinical characterization of seizures in newly referred adults*. Epilepsia, 1990. **31**(3): p. 292-301.
40. Olafsson, E., et al., *Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study*. Lancet Neurol, 2005. **4**(10): p. 627-34.
41. Christensen, J., et al., *Incidence and prevalence of epilepsy in Denmark*. Epilepsy Res, 2007. **76**(1): p. 60-5.
42. Carpio, A. and W.A. Hauser, *Epilepsy in the developing world*. Curr Neurol Neurosci Rep, 2009. **9**(4): p. 319-26.
43. Mignard, C., et al., *Incidence of newly diagnosed epileptic seizures in a French South Indian Ocean Island, La Reunion (EPIREUN)*. Epilepsia, 2009. **50**(10): p. 2207-12.
44. Winkler, A.S., et al., *Prevalence, incidence, and clinical characteristics of epilepsy--a community-based door-to-door study in northern Tanzania*. Epilepsia, 2009. **50**(10): p. 2310-3.

45. Benamer, H.T. and D.G. Grosset, *A systematic review of the epidemiology of epilepsy in Arab countries*. *Epilepsia*, 2009. **50**(10): p. 2301-4.
46. Tuan, N.A., et al., *The incidence of epilepsy in a rural district of Vietnam: a community-based epidemiologic study*. *Epilepsia*, 2010. **51**(12): p. 2377-83.
47. Celikkas, E., et al., *Incidence of epilepsy in a defined area of Central Anatolia, Turkey, after 15 years of age*. *Neuroepidemiology*, 2010. **35**(3): p. 221-5.
48. Banerjee, T.K., et al., *A longitudinal study of epilepsy in Kolkata, India*. *Epilepsia*, 2010. **51**(12): p. 2384-91.
49. Joensen, P., *Prevalence, incidence, and classification of epilepsy in the Faroes*. *Acta Neurol Scand*, 1986. **74**(2): p. 150-5.
50. Keranen, T., P.J. Riekkinen, and M. Sillanpaa, *Incidence and prevalence of epilepsy in adults in eastern Finland*. *Epilepsia*, 1989. **30**(4): p. 413-21.
51. Sidenvall, R., et al., *A community-based prospective incidence study of epileptic seizures in children*. *Acta Paediatr*, 1993. **82**(1): p. 60-5.
52. Olafsson, E., et al., *Incidence of epilepsy in rural Iceland: a population-based study*. *Epilepsia*, 1996. **37**(10): p. 951-5.
53. Jallon, P., et al., *Incidence of first epileptic seizures in the canton of Geneva, Switzerland*. *Epilepsia*, 1997. **38**(5): p. 547-52.
54. Annegers, J.F., et al., *The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations*. *Epilepsia*, 1999. **40**(4): p. 502-6.
55. MacDonald, B.K., et al., *The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK*. *Brain*, 2000. **123** (Pt 4): p. 665-76.
56. Oun, A., S. Haldre, and M. Magi, *Incidence of adult epilepsy in Estonia*. *Acta Neurol Scand*, 2003. **108**(4): p. 245-51.
57. Christensen J, V.M., Pedersen M G, Pedersen C B, Olsen J, Sidenius P, *Incidence and prevalence of epilepsy in Denmark*. *Epilepsy Research*, 2007. **76**: p. 60-65.
58. Casetta, I., et al., *Incidence of childhood and adolescence epilepsy: a community-based prospective study in the province of Ferrara and in Copparo, Italy, 1996-2005*. *Eur J Neurol*, 2011.
59. Everitt, A.D. and J.W. Sander, *Incidence of epilepsy is now higher in elderly people than children*. *Bmj*, 1998. **316**(7133): p. 780.
60. Sillanpaa, M., et al., *Temporal changes in the incidence of epilepsy in Finland: nationwide study*. *Epilepsy Res*, 2006. **71**(2-3): p. 206-15.
61. Sillanpaa, M., et al., *Regional differences and secular trends in the incidence of epilepsy in Finland: A nationwide 23-year registry study*. *Epilepsia*, 2011.
62. Lavados, J., et al., *A descriptive study of epilepsy in the district of El Salvador, Chile, 1984-1988*. *Acta Neurol Scand*, 1992. **85**(4): p. 249-56.
63. Rwiza, H.T., et al., *Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community-based study*. *Epilepsia*, 1992. **33**(6): p. 1051-6.
64. Tekle-Haimanot, R., L. Forsgren, and J. Ekstedt, *Incidence of epilepsy in rural central Ethiopia*. *Epilepsia*, 1997. **38**(5): p. 541-6.
65. Li, S.Z., *Epidemiologic study of epilepsy in six cities in China*. *Zhonghua Shen Jing Jing Shen Ke Za Zhi*, 1986. **19**(4): p. 193-6.
66. Aicardi, J., *Diseases of the Nervous system in Childhood. Epilepsy and other seizure disorders*. *Epilepsy and other seizure disorders*. 1992, London: Mac Keith Press.
67. Jennett, B., D. Teather, and S. Bennie, *Epilepsy after head injury. Residual risk after varying fit-free intervals since injury*. *Lancet*, 1973. **2**(7830): p. 652-3.
68. Goulden, K.J., et al., *Epilepsy in children with mental retardation: a cohort study*. *Epilepsia*, 1991. **32**(5): p. 690-7.

69. Austin, J.K., et al., *Behavior problems in children before first recognized seizures*. Pediatrics, 2001. **107**(1): p. 115-22.
70. Hesdorffer, D.C., et al., *ADHD as a risk factor for incident unprovoked seizures and epilepsy in children*. Arch Gen Psychiatry, 2004. **61**(7): p. 731-6.
71. Ferguson, P.L., et al., *A population-based study of risk of epilepsy after hospitalization for traumatic brain injury*. Epilepsia, 2010. **51**(5): p. 891-8.
72. Lowenstein, D.H., *Epilepsy after head injury: an overview*. Epilepsia, 2009. **50 Suppl 2**: p. 4-9.
73. Annegers John F, H.A.W., Coan Sharon P, Rocca Walter A, *A population-based study of seizures after traumatic brain injuries*. The New England Journal of Medicine, 1998. **338**(1): p. 20-24.
74. Annegers, J.F., et al., *The risk of unprovoked seizures after encephalitis and meningitis*. Neurology, 1988. **38**(9): p. 1407-10.
75. Dam, A.M., et al., *Late-onset epilepsy: etiologies, types of seizure, and value of clinical investigation, EEG, and computerized tomography scan*. Epilepsia, 1985. **26**(3): p. 227-31.
76. Luhdorf, K., L.K. Jensen, and A.M. Plesner, *Etiology of seizures in the elderly*. Epilepsia, 1986. **27**(4): p. 458-63.
77. Roberts, M.A., J.W. Godfrey, and F.I. Caird, *Epileptic seizures in the elderly: I. Aetiology and type of seizure*. Age Ageing, 1982. **11**(1): p. 24-8.
78. Sung, C.Y. and N.S. Chu, *Epileptic seizures in thrombotic stroke*. J Neurol, 1990. **237**(3): p. 166-70.
79. Hornig, C.R., et al., *Epileptic seizures following ischaemic cerebral infarction. Clinical picture, CT findings and prognosis*. Eur Arch Psychiatry Neurol Sci, 1990. **239**(6): p. 379-83.
80. Li, X., et al., *Vascular determinants of epilepsy: the Rotterdam Study*. Epilepsia, 1997. **38**(11): p. 1216-20.
81. Hauser, W.A., et al., *Seizures and myoclonus in patients with Alzheimer's disease*. Neurology, 1986. **36**(9): p. 1226-30.
82. Heaney, D.C., et al., *Socioeconomic variation in incidence of epilepsy: prospective community based study in south east England*. Bmj, 2002. **325**(7371): p. 1013-6.
83. Hesdorffer, D.C., et al., *Socioeconomic status is a risk factor for epilepsy in Icelandic adults but not in children*. Epilepsia, 2005. **46**(8): p. 1297-303.
84. Forsgren, L.a.L.N., *An incident case-referent study of epileptic seizures in adults*. Epilepsy Res, 1990. **6**: p. 66-81.
85. Duchowny MS, B.B., *Coexisting disorders in children with epilepsy*. Adv Stud Med, 2003. **3**: p. S680-S683.
86. Gijsen, R., et al., *Causes and consequences of comorbidity: a review*. J Clin Epidemiol, 2001. **54**(7): p. 661-74.
87. Gaitatzis, A., et al., *The epidemiology of the comorbidity of epilepsy in the general population*. Epilepsia, 2004. **45**(12): p. 1613-22.
88. Tellez-Zenteno J F, M.S., Wiebe S, *Somatic Comorbidity of epilepsy in the general population in Canada*. Epilepsia, 2005. **46**(12): p. 1955-1962.
89. Ottman, R., et al., *Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey*. Epilepsia, 2011. **52**(2): p. 308-15.
90. Sidenvall, R., L. Forsgren, and J. Heijbel, *Prevalence and characteristics of epilepsy in children in northern Sweden*. Seizure, 1996. **5**(2): p. 139-46.
91. Vingerhoets, G., *Cognitive effects of seizures*. Seizure, 2006. **15**(4): p. 221-6.
92. Konda, K., et al., *Health behaviors and conditions of persons with epilepsy: a bivariate analysis of 2006 BRFSS data*. Epilepsy Behav, 2009. **16**(1): p. 120-7.

93. Strine, T.W., et al., *Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey*. *Epilepsia*, 2005. **46**(7): p. 1133-9.
94. Shackleton, D.P., et al., *Living with epilepsy: long-term prognosis and psychosocial outcomes*. *Neurology*, 2003. **61**(1): p. 64-70.
95. Smeets, V.M., et al., *Epilepsy and employment: literature review*. *Epilepsy Behav*, 2007. **10**(3): p. 354-62.
96. Schupf, N. and R. Ottman, *Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: social and biologic influences*. *Epilepsia*, 1994. **35**(4): p. 750-6.
97. Sukumaran, S.C., P.S. Sarma, and S.V. Thomas, *Polytherapy increases the risk of infertility in women with epilepsy*. *Neurology*, 2010. **75**(15): p. 1351-5.
98. Lindsten, H., L. Nystrom, and L. Forsgren, *Mortality risk in an adult cohort with a newly diagnosed unprovoked epileptic seizure: a population-based study*. *Epilepsia*, 2000. **41**(11): p. 1469-73.
99. Loiseau, J., M.C. Picot, and P. Loiseau, *Short-term mortality after a first epileptic seizure: a population-based study*. *Epilepsia*, 1999. **40**(10): p. 1388-92.
100. Olafsson, E., W.A. Hauser, and G. Gudmundsson, *Long-term survival of people with unprovoked seizures: a population-based study*. *Epilepsia*, 1998. **39**(1): p. 89-92.
101. Neligan, A., et al., *The long-term risk of premature mortality in people with epilepsy*. *Brain*, 2011. **134**(Pt 2): p. 388-95.
102. Nilsson, L., et al., *Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy*. *Epilepsia*, 1997. **38**(10): p. 1062-8.
103. Hesdorffer, D.C., et al., *Combined analysis of risk factors for SUDEP*. *Epilepsia*, 2011. **52**(6): p. 1150-9.
104. Sillanpaa, M. and S. Shinnar, *Long-term mortality in childhood-onset epilepsy*. *N Engl J Med*, 2010. **363**(26): p. 2522-9.
105. Mu, J., et al., *Causes of death among people with convulsive epilepsy in rural West China: a prospective study*. *Neurology*, 2011. **77**(2): p. 132-7.
106. Tellez-Zenteno, J.F., R. Nguyen, and L. Hernandez-Ronquillo, *[Injuries, accidents and mortality in epilepsy: a review of its prevalence risk factors and prevention]*. *Rev Invest Clin*, 2010. **62**(5): p. 466-79.
107. Sheth, S.G., et al., *Mortality in epilepsy: driving fatalities vs other causes of death in patients with epilepsy*. *Neurology*, 2004. **63**(6): p. 1002-7.
108. Stephen, L.J. and M.J. Brodie, *Selection of antiepileptic drugs in adults*. *Neurol Clin*, 2009. **27**(4): p. 967-92.
109. Marson, A., et al., *Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial*. *Lancet*, 2005. **365**(9476): p. 2007-13.
110. Leone, M.A., A. Solari, and E. Beghi, *Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy*. *Neurology*, 2006. **67**(12): p. 2227-9.
111. Perucca, E. and T. Tomson, *The pharmacological treatment of epilepsy in adults*. *Lancet Neurol*, 2011. **10**(5): p. 446-56.
112. Kwan, P. and M.J. Brodie, *Early identification of refractory epilepsy*. *N Engl J Med*, 2000. **342**(5): p. 314-9.
113. Lindsten, H., H. Stenlund, and L. Forsgren, *Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure*. *Epilepsia*, 2001. **42**(8): p. 1025-30.
114. Annegers, J.F., W.A. Hauser, and L.R. Elveback, *Remission of seizures and relapse in patients with epilepsy*. *Epilepsia*, 1979. **20**(6): p. 729-37.

115. Semah, F., et al., *Is the underlying cause of epilepsy a major prognostic factor for recurrence?* Neurology, 1998. **51**(5): p. 1256-62.
116. Linehan, C., et al., *Future directions for epidemiology in epilepsy.* Epilepsy Behav, 2011. **22**(1): p. 112-7.
117. Ngugi, A.K., et al., *Incidence of epilepsy: A systematic review and meta-analysis.* Neurology, 2011. **77**(10): p. 1005-12.
118. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research.* Eur J Epidemiol, 2009. **24**(11): p. 659-67.
119. National, C.I. (2008) *Surveillance, epidemiology, and results; standard populations -19 age groups.* . <http://seer.cancer.gov/stdpopulations/stdpop.19ages.html> Accessed April 15, 2008
120. Morris, J.A. and M.J. Gardner, *Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates.* Br Med J (Clin Res Ed), 1988. **296**(6632): p. 1313-6.
121. Bruzzi, P., et al., *Estimating the population attributable risk for multiple risk factors using case-control data.* Am J Epidemiol, 1985. **122**(5): p. 904-14.
122. Greenland S, R.K., Lash TL, *Measures of effect and measures of association.* Third ed. ed. Modern Epidemiology,. 2008, Philadelphia: Lippincott Williams & Wilkins 67.
123. Vezzani, A., et al., *The role of inflammation in epilepsy.* Nat Rev Neurol, 2011. **7**(1): p. 31-40.
124. Martinez-Juarez, I.E., et al., *Epilepsy and multiple sclerosis: Increased risk among progressive forms.* Epilepsy Res, 2009. **84**(2-3): p. 250-3.
125. Striano, P., et al., *Epileptic seizures in multiple sclerosis: clinical and EEG correlations.* Neurol Sci, 2003. **24**(5): p. 322-8.
126. Nicoletti, A., et al., *Epilepsy and multiple sclerosis in Sicily: a population-based study.* Epilepsia, 2003. **44**(11): p. 1445-8.
127. Andrade, R.M., et al., *Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV).* Ann Rheum Dis, 2008. **67**(6): p. 829-34.
128. Dalman, C., et al., *Young cases of schizophrenia identified in a national inpatient register--are the diagnoses valid?* Soc Psychiatry Psychiatr Epidemiol, 2002. **37**(11): p. 527-31.
129. Makikyro, T., et al., *Accuracy of register-based schizophrenia diagnoses in a genetic study.* Eur Psychiatry, 1998. **13**(2): p. 57-62.
130. Alhlborn A, N.R., *Application of diagnostic criteria in the diagnosis of myocardial infarction.* Scand J Soc Med, 1979. **7**(2): p. 67-72.
131. Hammar, N., et al., *Identification of cases of myocardial infarction: hospital discharge data and mortality data compared to myocardial infarction community registers.* Int J Epidemiol, 1991. **20**(1): p. 114-20.
132. Braathen, G. and K. Theorell, *A general hospital population of childhood epilepsy.* Acta Paediatr, 1995. **84**(10): p. 1143-6.
133. Jallon, P., et al., *EPIMART: prospective incidence study of epileptic seizures in newly referred patients in a French Caribbean island (Martinique).* Epilepsia, 1999. **40**(8): p. 1103-9.
134. Zarrelli, M.M., et al., *Incidence of epileptic syndromes in Rochester, Minnesota: 1980-1984.* Epilepsia, 1999. **40**(12): p. 1708-14.
135. Freitag, C.M., et al., *Incidence of epilepsies and epileptic syndromes in children and adolescents: a population-based prospective study in Germany.* Epilepsia, 2001. **42**(8): p. 979-85.

136. Medina, M.T., et al., *Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salama Study*. *Epilepsia*, 2005. **46**(1): p. 124-31.
137. Wirrell, E.C., et al., *Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study*. *Epilepsy Res*, 2011. **95**(1-2): p. 110-8.
138. Kotsopoulos, I.A., et al., *Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures*. *Epilepsia*, 2002. **43**(11): p. 1402-9.
139. Sander, J.W., et al., *National General Practice Study of Epilepsy: newly diagnosed epileptic seizures in a general population*. *Lancet*, 1990. **336**(8726): p. 1267-71.
140. Manford, M., et al., *The National General Practice Study of Epilepsy. The syndromic classification of the International League Against Epilepsy applied to epilepsy in a general population*. *Arch Neurol*, 1992. **49**(8): p. 801-8.
141. Lancman ME, G.A., Norscini J, Granillo R, *Risk factors for developing seizures after stroke*. *Epilepsia*, 1993. **34**(1): p. 141-143.
142. Paolucci, S., et al., *Poststroke late seizures and their role in rehabilitation of inpatients*. *Epilepsia*, 1997. **38**(3): p. 266-70.
143. Kammersgaard, L.P. and T.S. Olsen, *Poststroke epilepsy in the Copenhagen stroke study: incidence and predictors*. *J Stroke Cerebrovasc Dis*, 2005. **14**(5): p. 210-4.
144. Lossius, M.I., et al., *Incidence and predictors for post-stroke epilepsy. A prospective controlled trial. The Akershus stroke study*. *Eur J Neurol*, 2002. **9**(4): p. 365-8.
145. Lamy, C., et al., *Early and late seizures after cryptogenic ischemic stroke in young adults*. *Neurology*, 2003. **60**(3): p. 400-4.
146. Gupta, S.R., et al., *Postinfarction seizures. A clinical study*. *Stroke*, 1988. **19**(12): p. 1477-81.
147. So, E.L., et al., *Population-based study of seizure disorders after cerebral infarction*. *Neurology*, 1996. **46**(2): p. 350-5.
148. Burn, J., et al., *Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project*. *Bmj*, 1997. **315**(7122): p. 1582-7.
149. Berges, S., et al., *Seizures and epilepsy following strokes: recurrence factors*. *Eur Neurol*, 2000. **43**(1): p. 3-8.
150. Lossius, M.I., et al., *Poststroke epilepsy: occurrence and predictors--a long-term prospective controlled study (Akershus Stroke Study)*. *Epilepsia*, 2005. **46**(8): p. 1246-51.
151. Benn, E.K., et al., *Estimating the incidence of first unprovoked seizure and newly diagnosed epilepsy in the low-income urban community of Northern Manhattan, New York City*. *Epilepsia*, 2008. **49**(8): p. 1431-9.
152. Mazza, M., et al., *Bipolar disorder and epilepsy: a bidirectional relation? Neurobiological underpinnings, current hypotheses, and future research directions*. *Neuroscientist*, 2007. **13**(4): p. 392-404.
153. Hesdorffer, D.C., et al., *Depression and suicide attempt as risk factors for incident unprovoked seizures*. *Ann Neurol*, 2006. **59**(1): p. 35-41.
154. Nilsson, L., et al., *Risk factors for suicide in epilepsy: a case control study*. *Epilepsia*, 2002. **43**(6): p. 644-51.
155. Stefanello, S., et al., *Psychiatric comorbidity and suicidal behavior in epilepsy: a community-based case-control study*. *Epilepsia*, 2010. **51**(7): p. 1120-5.
156. Mainio, A., et al., *Depression and suicide in epileptic victims: a population-based study of suicide victims during the years 1988-2002 in northern Finland*. *Epilepsy Behav*, 2007. **11**(3): p. 389-93.
157. Christensen, J., et al., *Epilepsy and risk of suicide: a population-based case-control study*. *Lancet Neurol*, 2007. **6**(8): p. 693-8.

158. Ettinger, A.B., *Psychotropic effects of antiepileptic drugs*. Neurology, 2006. **67**(11): p. 1916-25.
159. Schmitz, B., *Effects of antiepileptic drugs on mood and behavior*. Epilepsia, 2006. **47 Suppl 2**: p. 28-33.
160. Olesen, J.B., et al., *Antiepileptic drugs and risk of suicide: a nationwide study*. Pharmacoepidemiol Drug Saf, 2010. **19**(5): p. 518-24.
161. Alper, K., et al., *Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports*. Biol Psychiatry, 2007. **62**(4): p. 345-54.
162. Karouni, M., et al., *Psychiatric comorbidity in patients with epilepsy: a population-based study*. Eur J Clin Pharmacol, 2010. **66**(11): p. 1151-60.
163. Kondziella, D., et al., *Which clinical and experimental data link temporal lobe epilepsy with depression?* J Neurochem, 2007. **103**(6): p. 2136-52.
164. Kanner, A.M., *Depression and epilepsy: do glucocorticoids and glutamate explain their relationship?* Curr Neurol Neurosci Rep, 2009. **9**(4): p. 307-12.
165. Chang, Y.T., et al., *Bidirectional relation between schizophrenia and epilepsy: A population-based retrospective cohort study*. Epilepsia, 2011.
166. Kanner, A.M., *Epilepsy, suicidal behaviour, and depression: do they share common pathogenic mechanisms?* Lancet Neurol, 2006. **5**(2): p. 107-8.
167. Bagdy, G., et al., *Serotonin and epilepsy*. J Neurochem, 2007. **100**(4): p. 857-73.
168. Hedlund, P.B., *The 5-HT₇ receptor and disorders of the nervous system: an overview*. Psychopharmacology (Berl), 2009. **206**(3): p. 345-54.
169. Appenzeller, S., F. Cendes, and L.T. Costallat, *Epileptic seizures in systemic lupus erythematosus*. Neurology, 2004. **63**(10): p. 1808-12.
170. Gonzalez-Duarte, A., et al., *Clinical description of seizures in patients with systemic lupus erythematosus*. Eur Neurol, 2008. **59**(6): p. 320-3.
171. Brey, R.L., E. Muscal, and J. Chapman, *Antiphospholipid antibodies and the brain: a consensus report*. Lupus, 2011. **20**(2): p. 153-7.
172. Mikdashi, J., A. Krumholz, and B. Handwerker, *Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus*. Neurology, 2005. **64**(12): p. 2102-7.
173. Olafsson, E., J. Benedikz, and W.A. Hauser, *Risk of epilepsy in patients with multiple sclerosis: a population-based study in Iceland*. Epilepsia, 1999. **40**(6): p. 745-7.
174. Poser, C.M. and V.V. Brinar, *Epilepsy and multiple sclerosis*. Epilepsy Behav, 2003. **4**(1): p. 6-12.
175. Moreau, T., et al., *Epilepsy in patients with multiple sclerosis: radiological-clinical correlations*. Epilepsia, 1998. **39**(8): p. 893-6.
176. Engelsens, B.A. and M. Gronning, *Epileptic seizures in patients with multiple sclerosis. Is the prognosis of epilepsy underestimated?* Seizure, 1997. **6**(5): p. 377-82.
177. Kelley, B.J. and M. Rodriguez, *Seizures in patients with multiple sclerosis: epidemiology, pathophysiology and management*. CNS Drugs, 2009. **23**(10): p. 805-15.
178. Ramsey-Goldman, R., et al., *Time to seizure occurrence and damage in PROFILE, a multi-ethnic systemic lupus erythematosus cohort*. Lupus, 2008. **17**(3): p. 177-84.
179. Spatt, J., R. Chaix, and B. Mamoli, *Epileptic and non-epileptic seizures in multiple sclerosis*. J Neurol, 2001. **248**(1): p. 2-9.
180. Eriksson, M., E. Ben-Menachem, and O. Andersen, *Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis*. Mult Scler, 2002. **8**(6): p. 495-9.

