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The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in Cork city and county during the calendar year 2017

Volume 1 of 1

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Signed_____

Date_____

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List of Abbreviations

A.E.D.- Antiepileptic drug

C.N.S.-Clinical Nurse Specialist

C.R.E.C.- Clinical Research Ethics Committee

C.S.O.- Central Statistics Office

C.T.- Computed Tomography

E.C.G.- Electrocardiogram

El.D.- Electorial Division

E.D.- Emergency Department

E.E.G.- Electroencephalogram

I.L.A.E.- International League Against Epilepsy

I.Q.R.- Interquartile Range

I.R.- Incidence Ratio

G.D.P.R.- General Data Protection Regulator

G.P.- General Practitioner

H.I.P.E.- Hospital In-Patient Enquiry System

H.H.S.- Hyperglycaemic Hyperosmolar State

M.E.S.S.- Multicentre Trial for Early Epilepsy and Single Seizures

M.R.N.- Medical Record Number

M.R.I.- Magnetic Resonance Imaging

R.A.S.C.- Rapid Access Seizure Clinic

R.D.I.- Relative Deprivation Index

S.T.R.O.N.D.- Standards of Reporting of Neurological Disorders

U.S.A.- United States of America

U.K.- United Kingdom

95% CI- Ninety five percent confidence interval

Chapter 1 Introduction

1.1 Study overview

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of the condition.[1] Globally, epilepsy is a notable cause of disability and mortality[2] and poses a substantial economic burden for health care systems, individuals and their families through direct costs of treatment and indirect costs such as loss of productivity and employment. Epidemiologic studies of epilepsy are necessary to define the full public health burden of epilepsy within a population and to set public health and health care priorities.[3]

Previously reported epidemiological studies vary in their methodology and detail of reporting and it is not always possible to compare or infer information from different geographic regions. Standardisation of epidemiologic methodology, detailed reporting of results and further studies from geographic regions lacking data have been called for.[2-4] We aimed to undertake the first epidemiologic study in Ireland investigating the incidence of first seizures, epilepsy and seizure mimics within the geographically defined area of Cork city and county, in accordance with up-to-date international definitions and classifications of epilepsy[5-7] and international guidelines for epidemiologic studies[3, 8] in order to address gaps in knowledge, and to investigate the effect of updated international definitions on the epidemiologic study of epilepsy.

1.2 Epidemiologic terminology

Epidemiologic studies use a number of different measures to assess a disease within a population. The prevalence of epilepsy is defined as the proportion of a population with a diagnosis of epilepsy at a specified timepoint.[9] It may be further divided into active and lifetime prevalence, representing those who continue to have recurrent seizures or are maintained on antiepileptic drugs (A.E.D.s) versus those who have ever had a diagnosis of epilepsy, regardless of current seizure occurrence or A.E.D. use. Prevalence data are therefore useful to estimate the burden of the disease within a population, which in turns informs resource allocation.

In contrast, the cumulative incidence of epilepsy is the proportion of people who *develop* epilepsy during a specified time, usually one year.[9] Incidence cohorts provide the most comprehensive information on aetiology, natural history, prognosis and comorbidities associated with a disease because they include those who will die shortly after diagnosis, as well as those who will enter remission quickly, both of whom may be missed in prevalence studies. Prevalence studies, therefore, may overrepresent the characteristics of enduring cases.

Worldwide, incidence studies are conducted less often than prevalence studies, perhaps due to the difficulty and expense of identifying the incident cohort. More detailed and precise incidence studies, providing information on seizure type and etiology using rigorous methods of case ascertainment, have been encouraged[2-4] to address gaps in our current understanding.

1.3 Epidemiology of epilepsy

A recent meta-analysis of incidence studies of epilepsy highlighted significant heterogeneity between studies.[4] Estimated pooled annual cumulative incidence of epilepsy, based on 14 studies, was reported as 67.8

per 100,000 persons [95% confidence interval (95%CI) 56.6 to 81.0] with one outlier report of 189.96 per 100,000. However, this outlier refers to a study reporting incidence of all first epileptic seizures in Ecuador,[10] including both provoked and unprovoked seizures, rather than epilepsy *per se*, which could have skewed the results.

Reported results from different populations may vary because of different definitions used to define epilepsy, as outlined above, rather than true population risk differences. Accuracy and validity of results are also dependent on maximization of case ascertainment and accuracy of case identification. Methods of case ascertainment in published studies range from door-to-door population surveys,[11-16] to sole use of administrative medical record linkage databases,[17-22] to use of multiple overlapping methods[23-25] thus providing variations in maximization of case ascertainment and the ability of investigators to verify clinical diagnosis. Specific details such as aetiology and classification of epilepsy may not be available, depending on the methodology used. Table 1.1 compares published whole population studies investigating new onset epilepsy in terms of methodologies used, availability of specific case information and reported crude and age-adjusted incidence results. Table 1.2 compares whole population studies reporting incidence of first epileptic seizures and Table 1.3 compares whole population studies investigating first provoked seizures.

1.4 International guidelines for epidemiologic studies of epilepsy

In 2011, in an effort to promote consistency in definitions and methods used in epidemiologic studies, and to facilitate comparisons between populations, the International League Against Epilepsy (I.L.A.E.) proposed standards for epidemiologic studies and surveillance of epilepsy.[3] These guidelines emphasize the importance of using multiple overlapping methods to maximize the sensitivity of case ascertainment. Furthermore, Standards of

Reporting of Neurological Disorders (S.T.R.O.N.D.) guidelines[8] for reporting of incidence and prevalence studies in neuroepidemiology have been developed to facilitate better reporting of published data and allow comparisons between studies, see Appendix 1 for S.T.R.O.N.D. checklist. When applied, these guidelines enhance population-based epidemiologic studies and encourage the collection of data useful for the promotion of public health.

1.5 I.L.A.E. definitions

The 2005 I.L.A.E. definition of an epileptic seizure is as follows:

- An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[1]

The 2005 I.L.A.E. conceptual definition of epilepsy is as follows:

- Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of the condition. The definition of epilepsy requires at least one epileptic seizure. [1]

Therefore, conceptually, epilepsy exists after at least one epileptic seizure when there is a high risk for another. However, the magnitude of the “high risk” was previously under debate. Prior to 2014, in both epidemiologic studies and clinical practice, the diagnosis of epilepsy required two or more unprovoked seizures occurring at least 24 hours apart.[26] In 2014, the I.L.A.E. updated its *operational* definition of epilepsy[5] as follows:

- Epilepsy is a disease of the brain defined by any of the following conditions: i) at least two unprovoked (or reflex) seizures occurring >24 hours apart ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or iii) diagnosis of an epilepsy syndrome.[5]

This significant change was instigated in order to recognise and validate the relatively common clinical scenario whereby some people, following a single unprovoked seizure, are known to be at increased risk of recurrence. The I.L.A.E., by allowing clinicians to diagnose epilepsy in these patients at an earlier timepoint, rather than waiting for the second seizure, supports commencing them on an A.E.D., and therefore, at least in the short term, reducing the risk of further seizures. An increased risk of more than 60% was used because natural history studies had shown that following two unprovoked seizures, the chance of a third within four years was 73% with a 95% CI of 59-87%.[27] However, quantifying the risk of a second seizure in a patient who presents with a first unprovoked seizure is very challenging, even for experienced clinicians. In acknowledgement of this, the 2014 I.L.A.E. operational definition does not require the clinician to estimate the risk precisely. This flexibility is necessary in clinical practice, but provides potential further challenges to standardising diagnosis of epilepsy within populations and therefore has a potentially significant impact on future epidemiologic research.

For symptomatic seizures, the following 2010 I.L.A.E. definition was used:

- Acute symptomatic seizures are epileptic seizures which occur in close temporal association with an acute systemic, metabolic or toxic insult or in association with an acute central nervous system insult.[28] The interval between the insult and the seizure may vary according to the underlying clinical condition, see Table 1.4.

1.6 Updated I.L.A.E. classification systems for seizures and epilepsy

In 2017, the I.L.A.E. revised its classification system for seizures[6] and epilepsy[7] types to reflect advances in knowledge regarding the underlying mechanism of epilepsy. Prior to this, the classification system in use, in modified form, dated from 1981.[29] According to the updated systems, seizures are classified as either focal onset, generalized onset or unknown onset, and persons with epilepsy have either focal epilepsy, generalized epilepsy, a combination of focal and generalized epilepsy or unknown classification of epilepsy based on their seizure type. Allowing a seizure classification group of unknown onset marks an important distinction from the previous I.L.A.E. classification system, which did not allow easy classification of seizures when onset was unknown. Therefore, the previous system may have resulted in tonic-clonic seizures with an unwitnessed or unclear onset being classified as generalized in nature, based purely on their clinical characteristics. Importantly, the 2017 classification systems allow clinicians to incorporate information from electroencephalogram (E.E.G) and brain imaging into the classification of a person's seizures and epilepsy.

1.7 Seizure mimics

Assessment of patients presenting with first seizures is critical to differentiating epileptic seizures from other conditions that they resemble. An early study by Loiseau et al.,[30] demonstrates well the potential for misdiagnosis in epidemiologic studies. Following case ascertainment using a screening questionnaire to neurologists and electroencephalographers, 952 potential cases were identified, resulting in an annual incidence of 84.5 per 100,000. Following review of medical records, 135 cases were excluded for incorrect diagnosis, the most common being syncopal events. Further follow-up at one year resulted in exclusion of a further 33 cases as misdiagnosis of epilepsy, resulting in a final reported incidence of 71.3 per 100,000.

A 2005 study from 26 general practices in the United Kingdom (U.K.) [31] reported misdiagnosis in 16.3% of patients registered with a diagnosis of epilepsy and prescribed A.E.D.s following assessment at a specialist epilepsy clinic. A systematic review of 26 studies[32] reported the frequency of false positive diagnosis of epilepsy in 6912 people with epilepsy. In total, 1249 persons were given an incorrect diagnosis of epilepsy. Misdiagnosis varied from 2 to 71% from a variety of clinical settings, see Table 1.5. Due to heterogeneity across studies, quantitative meta-analysis was impossible. Syncope and psychogenic non-epileptic seizures were the most commonly reported mimics, representing 52.4% and 34.7% of total misdiagnosed cases, respectively.

False positive diagnosis of epilepsy can result in long-term prescription of potentially harmful A.E.D.s [33] as well as potential social consequences from driving[33] and work restrictions[34] and therefore it is important for potential cases to be assessed early. Diagnosis of a seizure mimic requires careful clinical assessment, and often specific investigations, thus placing a burden on health care resources. Despite the extent of misdiagnosis, to our knowledge there are no published epidemiologic studies on seizure mimics.

1.8 Sociodemographic information

Studies have shown an association between social deprivation and prevalence of epilepsy.[35-37] Higher prevalence of epilepsy among residents living in socially deprived areas may be due to social drift, or to social causation, whereby factors associated with social deprivation put an individual at risk of epilepsy,[38] or to a combination of both these factors. Incidence studies that calculate a level of social deprivation for persons at the time of their first seizure are necessary to establish if social deprivation is associated with the development of seizures and epilepsy and to identify and modify potential risk factors. Furthermore, if certain social groups have

a higher incidence of epilepsy, health care provision and resources should reflect the increased needs of these groups.

In 1990, a case-referent study from Northern Sweden investigating the incidence of unprovoked epileptic seizures in adults found no difference in sociodemographic factors between cases and controls.[39] More recently, a 2002 study in an unselected population served by 20 general practices in the U.K.,[40] demonstrated that the incidence of epilepsy in the most deprived fifth of the population was 2.33 times higher than the least deprived fifth using an index of social deprivation based on four variables available from census data. Further adjustment for whether the practice was in London attenuated the findings. However, this may represent over-adjustment given that populations served by the eight London practices were in more deprived areas. A strong correlation between epilepsy incidence and social deprivation, using a census based index of social deprivation, was reported in a Welsh medical record linkage study,[38] with annual incidence in the most deprived decile twice that of the least deprived decile. The aetiology and classification of epilepsy was not reported in either of these studies. Finally, a community-based study in New York carried out between 2003 and 2005 reported a higher incidence of unprovoked seizures in low-income compared to high-income households. [25]

Results from studies investigating the incidence of epilepsy in children in socially deprived areas have been conflicting. Using an area level measure of deprivation, no difference was found in the incidence of epilepsy across four quartiles of social deprivation in 155 children aged 29 days to 14 years old in the U.K.[41] In contrast, living in a high-deprivation neighbourhood in Sweden[42] increased the odds of hospital registration for childhood and adolescent epilepsy by 15% compared to those living in low-deprivation neighbourhoods. Finally, a case-control study from Iceland[43] found that low socioeconomic status, as measured by low individual-level educational attainment or lack of home ownership, increased the risk of incident epilepsy in adults, whereas no markers of socioeconomic status were

associated with incident epilepsy in children. To our knowledge no study to date has reported if the incidence of provoked seizures or of diagnosis with a seizure mimic differs between areas of relatively low and high social deprivation.

1.9 Epidemiologic data on epilepsy in Ireland

The incidence of epilepsy in an Irish population has not previously been investigated. The most comprehensive prevalence study of epilepsy in Ireland to date was published in 2010. Linehan et al.,[44] estimated that 10 per 1,000 persons aged 18 years and older had a self-reported lifetime prevalence of epilepsy. In addition, using a primary care reimbursement database for A.E.D.s, they estimated that 8.3-9.0 per 1,000 persons aged 5 years and older are being treated for epilepsy with A.E.D.s in Ireland. Though the response rate from general practice was low (22%), they estimated that the typical general practitioner (G.P.) provided care to an average of 13 patients with epilepsy. This study also included survey of consultant neurologists nationwide and estimated that specialist care is provided on a weekly basis to 442 persons with epilepsy nationally. Finally, using Hospital In-Patient Enquiry System (H.I.P.E) data, Linehan et al., reported that approximately 67 discharges are reported for persons with epilepsy from acute hospitals weekly in the Republic of Ireland. Calculating the incidence of epilepsy was beyond the scope of the study, nor did they acquire data on epilepsy type or aetiology. Two other studies have investigated prevalence in specific populations in Ireland. Based on review of E.E.G. databases in a tertiary hospital serving 1.1 million persons in the south of Ireland, Mullins et al., 2007,[45] reported the period prevalence of idiopathic generalized epilepsy at 35 per 100,000 persons over a three year period. McCarron et al., 2014[46] reported a point prevalence of epilepsy of 30.7% among persons aged 40 years or older who were registered to receive support for intellectual disability in Ireland. None of these studies included social deprivation as an aspect of their investigation.

In order to estimate what the incidence of epilepsy in Ireland might be, the 2000 study from MacDonald et al.,[47] in the U.K. currently serves as our nearest comparator. The investigators captured all new diagnosis of neurological disorders in an unselected urban population in London by rigorous survey of general practices and through a dedicated clinic at the National Hospital for Neurology and Neurosurgery. They reported the annual incidence of new diagnosis of epilepsy as 42 per 100,000 population, with 95% CI of 36-60. However, no further detail is available regarding aetiology and classification of epilepsy within this population. Furthermore, the urban environment of London may not be directly comparable to many areas in Ireland.

1.10 Research aims and objectives

The aim of this study is to investigate the incidence of all first seizures, new diagnosis of epilepsy and seizure mimics within the defined geographic area of Cork city and county during the calendar year 2017.

Objectives

- To maximise case ascertainment, in accordance with the I.L.A.E. epidemiologic guidelines,[3] within the confines of our health care service.
- To accurately validate and classify cases by review of individual case medical records and investigations, in accordance with I.L.A.E. epidemiologic guidelines[3] and I.L.A.E. seizure[6] and epilepsy[7] classification systems.
- To report in detail the age and gender specific incidence, risk factors and aetiology of unprovoked and provoked seizures and epilepsy within the defined geographic area.

- To investigate the effect of the updated I.L.A.E. operational definition of epilepsy[5] on the incidence of epilepsy within the defined geographic area.
- To investigate the association between the incidence of first seizures, new diagnosis of epilepsy and seizure mimics and socioeconomic deprivation within the defined geographic area.

This PhD thesis is presented in the format of 'PhD by publication', whereby each of the following Chapters 2 to 6 has been submitted, or is planned to be submitted, for publication as an original research article to a peer-reviewed scientific journal. Chapter 7 presents a summary and discussion of the PhD thesis as a whole and considers implications and areas for future research.

1.11 Tables

Table 1.1 Comparison of previous whole population studies, with regard to case ascertainment methodology used and reported results, investigating the incidence of epilepsy in different geographic areas.[1]

Study	Hernández-Ronquillo et al., 2018[22]	Giussani et al., 2014[48]	Houinato et al., 2012[49]	Winkler et al., 2009[16]	Benn et al., 2008[25]	Saha et al., 2008[50]	Christensen et al., 2007[20]	Olafsson et al., 2005[24]	Medina et al., 2005[15]	MacDonald et al., 2000[47]	Annegers et al., 1999[19]
Geographic area	Saskatchewan Canada	Lecco, Italy	Central Benin	Northern Tanzania	New York, U.S.A.	West Bengal	Denmark	Iceland	Salamá, Honduras	London, United Kingdom	Houston, Texas, U.S.A.
Population	1,033,381	311,637	11,668	41,937	270,677	20,727	6,543,341	882,151	6,473	100,230	c.600,000
Case ascertainment methods											
Radiology database								X			
E.E.G. database								X			
Emergency Department					X			X			
Neurologists/Paediatricians					X			X			
Other hospital specialists								X			
R.A.S.C.										X	
G.P. survey								X		X	
Residential care survey					X			X			
Hospital medical record data	X	X	X		X		X			X	X
Door to door survey			X	X		X			X		
School teachers and social workers			X								
Results reported											
Seizure/epilepsy type			Y	Y	Y	Y		Y	Y		
Aetiology				Y	Y	Y		Y	Y		Y
Risk factors			Y	Y							
Gender ratio	Y	Y	Y		Y	Y	Y	Y			
Age-specific incidence	Y	Y	Y	Y	Y	Y	Y	Y			Y
Crude annual cumulative incidence per 100,000 persons			69.4			36.66					
Crude incidence rate per 100,000 person-years	63	53.41		81	15.1		68.8	33.3	92.7		35.5
Age-adjusted incidence of epilepsy (per 100,000) 1993 I.L.A.E. definition	62 adjusted to Canada	44.74 adjusted to world			16.4 adjusted to U.S.	42.08 adjusted to world		32.4 adjusted to Europe		46 adjusted to U.K.	

[1] E.E.G.= electroencephalogram; G.P.= General Practitioner; R.A.S.C.-= Rapid access seizure clinic; U.K.= United Kingdom; U.S.A.= United States of America; X= Case method used in this study; Y=Yes, results available in this study.

Table 1.1 contd.Comparison of previous whole population studies, with regard to case ascertainment methodology used and reported results, investigating the incidence of epilepsy in different geographic areas.[2]

Study	Mani et al., 1998[14]	Tekle-Haimanot et al., 1997[13]	Olafsson 1996[51]	Hauser et al., 1993[52]	Lavados et al., 1992[18]	Rwiza et al., 1992[12]	Joensen 1986[53]	Li et al., 1985[11]	Granieri et al., 1983[23]	Hauser and Kurland, 1975[17]	De Graaf 1974[54]
Geographic area	Southern India	Rural Ethiopia	Rural Iceland	Rochester, U.S. A.	Northern Chile	Ulanga Tanzania	Faroe Island	China	Copparo, Italy	Rochester, U.S.A.	Northern Norway
Population	64,963	61,686	90,237	c.40,000	18,051	18,183	41,144	63,195	46,336	c.34,678	215,000
Case ascertainment methods											
Radiology database											
E.E.G. database			X				X		X		X
Emergency Department											
Neurologists/Paediatricians			X						X		
Other hospital specialists											
R.A.S.C.											
G.P. survey							X		X		
Residential care survey											
Hospital medical record data			X	X	X				X	X	X
Door to door survey	X	X				X		X			
School teachers and social workers									X		
Results reported											
Seizure/epilepsy type		Y	Y	Y	Y	Y	Y	Y	Y	Y	
Aetiology		Y	Y	Y	Y	Y		Y	Y	Y	Y
Risk factors											
Gender ratio	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Age-specific incidence	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
Crude annual cumulative incidence per 100,000 persons	49.3	64	47			73.3	42.8	25	33.1	48.7	32.8
Crude incidence rate per 100,000 person-years					113						
Age-adjusted incidence of epilepsy (per 100,000) 1993 I.L.A.E. definition		49 adjusted to U.S.		44 adjusted to U.S.	108 adjusted to Chile	55 adjusted to US		35 adjusted to U.S	38.3 adjusted to Italy		

[2] E.E.G.= electroencephalogram; G.P.= General Practitioner; R.A.S.C.-= Rapid access seizure clinic; U.K.= United Kingdom; U.S.= United States of America; X= Case method used in this study; Y=Yes, results available in this study.

Table 1.2 Comparison of previous whole population studies, with regard to case ascertainment methodology used and reported results, investigating the incidence of all epileptic seizures in different geographic areas.[3]

Study	Hauser & Kurland, 1975[17]	Loiseau et al., 1990[30]	Placencia 1992[10]	Hauser et al., 1993[52]	Jallon et al. 1997[55]	Jallon et al.,1999[56]	Annegers et al., 1999[19]	MacDonald et al., 2000[47]	Olafsson et al., 2005[24]	Benn et al., 2008[25]	Mignard et al., 2009[57]	Stranjalis et al., 2009[58]	Verentzioti et al., 2017[59]
Geographic area (population)	Rochester, U.S.	Gironde, France	Equador highlands	Rochester, U.S.	Geneva, Switzerland	Martinique Island	Houston, Texas, U.S.A.	London, U.K.	Iceland	New York, U.S.A.	La Reunion Island	Corfu, Greece	Lesvos, Greece
Population	c.34,678	1,128,164	c.75 000	c. 40,000	384,657	383,596	c.600,000	100,230	882,151	270,677	763,204	113,479	86,436
Case ascertainment methods													
Radiology database									X				
E.E.G. database		X			X				X		X		
Emergency Department						X			X	X			X
Neurologists/Paediatricians		X			X	X			X	X	X	X	X
Other hospital specialists									X				
R.A.S.C.								X					
Clinical Nurse Specialist													
G.P. survey						X		X	X				X
Residential care survey									X	X			
Hospital medical record data	X			X			X	X		X			X
Door to door survey			X										
Results available													
Seizure/epilepsy type					Y				Y	Y	Y		Y
Aetiology			Y		Y	Y	Y		Y	Y	Y		Y
Risk factors									Y	Y			
Gender ratio	Y		Y		Y	Y			Y		Y	Y	Y
Age-specific incidence					Y	Y					Y		Y
All first seizures (provoked and unprovoked, single and recurrent)		71.3	122 min - 190max		71	80.6					100.4		52.1
First single unprovoked and first provoked	23.6												
All first unprovoked epileptic seizures(single and recurrent)				61	45.6	64.1	50.9		56.8	38.6	81.2		35.9
First single unprovoked seizure		18.3		c.17				11	23.5	23.9		32.6	
Age-adjusted annual incidence					69.4 adjusted to US	77.7 adjusted to US			55.2 adjusted to Europe		115.4 adjusted to US		

[3] E.E.G.= electroencephalogram; G.P.= General Practitioner; R.A.S.C.-= Rapid access seizure clinic; U.K.= United Kingdom; U.S.A.= United States of America; X= Case method used in this study; Y=Yes, results available in this study.

Table 1.3 Comparison of previous whole population studies, with regard to case ascertainment methodology used and reported results, investigating the incidence of acute symptomatic seizures in different geographic areas.[4]

Study	Loiseau et al., 1990[30]	Annegers et al. 1995[60]	Jallon et al., 1997[55]	Jallon et al., 1999[56]	Mignard et al., 2009[57]	Stranjalis et al., 2009[58]	Verentzioti et al., 2017[59]
Geographic area (population)	Gironde, SW France	Rochester, U.S.A.	Geneva, Switzerland	Martinique Island	La Reunion Island	Corfu, Greece	Lesvos, Greece
Population	1,128,164	c.40,000	384,657	383,596	763,204	113,479	86,436
Case ascertainment methods							
E.E.G. database	X		X		X		
Emergency Department				X			X
Neurologists/Paediatricians	X		X	X	X	X	X
G.P. survey				X			X
Social security foundation						X	
Hospital medical record data		X					X
Results available							
Aetiology	Y	Y	Y	Y	Y	Y	Y
Gender ratio		Y	Y	Y	Y		Y
Crude annual incidence of first provoked seizures per 100,000 population	29	35	25.2	16.4	17.7	27.3	16.2

[4] E.E.G.= electroencephalogram; G.P.= General Practitioner; U.S.A.= United States of America; X= Case method used in this study; Y=Yes, results available in this study.

Table 1.4 Examples of acute symptomatic seizures in association with disruption of the structural or functional integrity of the brain.

Adapted from the I.L.A.E. Standards for Epidemiologic Studies[3]

Cause	Period of occurence	Notes/exceptions
Cerebrovascular disease	First 7 days	
Traumatic brain injury	First 7 days	Included intracranial surgery. Longer intervals are acceptable for subdural haematoma in the absence of known trauma or at first identification of haematoma. Subsequent seizures are unprovoked.
CNS infection	First 7 days	Included seizures occuring after 7 days in patients with persistent clinical and/or laboratory signs of infection.
Cerebral tuberculoma	During treatment	Seizures occuring after successful treatment are unprovoked
Brain abscess	During treatment	Seizures occuring after successful treatment are unprovoked
HIV infection	Acute infection or severe metabolic disturbance	Seizures occuring in the absence of opportunistic CNS infection or severe metabolic disturbance are unprovoked
Arteriovenous malformation	In the presence of acute haemorrhage	All other seizures are unprovoked
Multiple sclerosis	First presenting symptom within 7 days of relapse	
Autoimmune disease	Signs or symptoms of activation	

Table 1.5 Observational studies of the frequency of false positive diagnosis of epilepsy

Includes 4 population based studies, 17 studies recruited from epilepsy centers or tertiary hospitals and 5 studies from tilt table or implantable E.C.G. recorder centers, adapted from Xu et al., 2016[32].[5]

First author, year	Region	Sample size (n)	False positive frequency (95% CI) (%)
Population based			
McCluggage 1984[61]	Northern Ireland	247	2 (0 to 4)
Labiner 2009[62]	Arizona, U.S.A.	171	8 (5 to 13)
Leach 2005[31]	Wrexham, U.K.	275	16 (12 to 21)
Scheepers 1998[63]	Cheshire, U.K.	214	22 (17 to 29)
Epilepsy centres or tertiary hospitals			
Karacan 2010[64]	Erzurum, Turkey	119	2 (0 to 5)
Viteva 2009[65]	Plovdiv, Bulgaria	191	2 (0 to 5)
Smith 2002[66]	Cardiff, U.K.	180	4 (1 to 7)
Stroink 2003[67]	Netherlands	412	4 (3 to 7)
Gibbs 1992[68]	Liverpool, U.K.	850	9 (7 to 11)
Miakotnykh 1990[69]	Yekaterinburg, Russia	635	11 (9 to 13)
Alsaadi 2004[70]	California, U.S.A.	113	18 (11 to 26)
Yogarajah 2009[71]	Buckinghamshire, U.K.	230	18 (14 to 24)
Josephson 2007[33]	Halifax, Canada	1506	19 (18 to 22)
King 1982[72]	Georgia, U.S.A.	60	20 (10 to 30)
Hovorka 2007[73]	Prague, Czech Republic	249	22 (17 to 28)
Betts 1992[74]	Birmingham, U.K.	343	23 (19 to 28)
Smith 1999[34]	Liverpool, U.K.	184	26 (20 to 32)
Faulkner 2012[75]	Sydney, Australia	210	31 (26 to 38)
Parra 1999[76]	Chicago, U.S.A.	28	35 (18 to 53)
Uldall 2006[77]	Denmark	223	39 (33 to 45)
Kutlu 2013[78]	Ankara, Turkey	105	54 (45 to 64)
Tilt testing of implantable E.C.G. centres			
Hamid 2009[79]	Salford, U.K.	62	12 (5 to 21)
Rangel 2014[80]	Porto, Portugal	94	33 (23 to 43)
Zaidi 2000[81]	Manchester, Chesbire and Salford, U.K.	74	41 (31 to 53)
LaRoche 2011[82]	Atlanta, U.S.A.	17	47 (23 to 71)
Edfors 2008[83]	Copenhagen, Denmark	120	71 (63 to 79)

[5] E.C.G.= electrocardiogram; U.K.= United Kingdom; U.S.A.= United States of America.

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Chapter 2 Methods

The first section of this chapter presents the study protocol applied to the geographically defined population as published in the 'Methods in Neuroepidemiology' section of the journal *Neuroepidemiology*:

Application of recent international epidemiological guidelines to a prospective study of the incidence of first seizures, newly-diagnosed epilepsy and seizure mimics in a defined geographic region in Ireland. EM Maloney, E Chaila, EJ O'Reilly, DJ Costello. Neuroepidemiology 2019;53(3-4):225-236.

In this paper, I present the first three months of data collection to demonstrate a successful and effective study protocol. In the second section of this chapter, for the purpose of this PhD thesis submission, I present the results of case ascertainment for the completed 15-month study protocol.

2.1 Application of recent international epidemiological guidelines to a prospective study of the incidence of first seizures, newly-diagnosed epilepsy and seizure mimics in a defined geographic region in Ireland

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Short title: Methodology of a prospective incidence study on epilepsy, seizures and mimics

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2.1.1 Abstract

Studies adherent to international guidelines and epilepsy classification are needed to accurately record the incidence of isolated seizures, epilepsy and seizure-mimics within a population. Because the diagnosis of epilepsy is largely made through clinical assessment by experienced physicians, seizures and epilepsy are susceptible to misdiagnosis. Previous epidemiological studies in epilepsy have not captured 'seizure mimics'. We therefore sought to quantify the incidence of isolated seizures, epilepsy and seizure-mimics using the International League Against Epilepsy (I.L.A.E.) classification system. In this study multiple overlapping methods of case ascertainment were applied to a defined geographic region from 1st January 2017 to 31st March 2017 to identify all patients presenting with first seizures (provoked and unprovoked), new diagnoses of epilepsy and seizure mimics. Over a three month period, from a population of 542,869 adults and children, 442 potential presentations were identified, and 283 met the inclusion criteria. Radiology databases were the source of the largest number of individual cases (n=153, 54%), while electroencephalogram (E.E.G.) databases were the source of the highest number of unique-to-source cases (those not identified elsewhere, n=60, 21%). No single case was picked up in every method of ascertainment. Among the 283 included presentations, 38 (13%) were classed as first provoked seizures, 27 (10%) as first unprovoked seizures, 95 (34%) as new diagnosis of epilepsy and 113 (40%) as seizure mimics. Ten (3%) presentations were indeterminate. We present and apply a rigorous study protocol for investigation of the incidence of first seizures, new diagnosis of epilepsy and seizure mimics in a geographically defined region which is adherent to recently published international guidelines for epidemiological studies and epilepsy classification. We highlight the challenges in making a diagnosis of new-onset epilepsy in patients presenting with a first seizure using the current I.L.A.E. definition of epilepsy, when epilepsy can be diagnosed in situations where the treating physician anticipates the risk of further seizures exceeds 60%.

2.1.2 Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition [1]. Operationally, epilepsy can be diagnosed in 3 circumstances: (i) at least 2 unprovoked (or reflex) seizures occurring more than 24 hours apart, (ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years, and (iii) diagnosis of an epilepsy syndrome [2]. The second situation is relatively common but difficult to apply in real life as judging that an individual patient has a 60% risk of further seizures is challenging. Epilepsy poses a substantial economic burden for health care systems, individuals and their families through direct costs of treatment and indirect costs such as loss of productivity and employment [3]. Epidemiological studies are necessary to define the full public health burden of epilepsy within a population, to provide information needed for early detection and treatment, and to set public health and health care priorities [4]. Assessment of patients presenting with first seizures is critical to differentiating epileptic seizures from other conditions that resemble epileptic seizures ('seizure mimics'). Although first seizures and epilepsy are susceptible to misdiagnosis, to our knowledge there are no published epidemiological studies on seizure mimics.

There are significant disparities in reported prevalence and incidence of epilepsy worldwide. While some variation may be related to factors such as socioeconomic class, access to healthcare, stigmatization and exposure to environmental risk factors [5], a significant contributor to the variation in reported incidence and prevalence may be due to heterogeneous methodologies used across studies. A recent meta-analysis of 48 incidence studies noted significant heterogeneity between studies. Estimated the pooled annual cumulative incidence of epilepsy, based on 14 studies, as 67.77 per 100,000 persons (95% confidence interval [CI] 56.6 to 81.0) with one outlier report of 189.96 per 100,000 [6]. Methods of case ascertainment in published studies

range from door-to-door population surveys, administrative database searches and surveys of neurology referral centers [7-9], thus providing variations in inclusion criteria and accuracy of case ascertainment. Many studies employ retrospective case ascertainment and lack of detailed diagnostic information often prohibits accurate classification of seizure and epilepsy type.

In 2011, in an effort to promote consistency in definitions and methods used in epidemiological studies and to facilitate comparisons between populations, the International League Against Epilepsy (I.L.A.E.) proposed standards for epidemiologic studies and surveillance of epilepsy [4]. These guidelines emphasize the importance of using multiple overlapping methods of case ascertainment to maximize the sensitivity of case ascertainment. Furthermore, Standards of Reporting of Neurological Disorders (S.T.R.O.N.D.) guidelines for reporting of incidence and prevalence studies in neuroepidemiology have been developed to facilitate better reporting of published data and allow comparisons between studies [10]. When applied to future studies, these guidelines will enhance population-based epidemiological studies and encourage the collection of data useful for the promotion of public health. Finally, the I.L.A.E. has recently commissioned updated classifications systems for both seizures and epilepsy types [11,12]. These classification systems are user-friendly and allow classification of seizure and epilepsy type by taking into account results of E.E.G. and imaging investigations. To our knowledge, this is the first epidemiological study to incorporate these classifications.

In Ireland, it has been estimated that 10 per 1,000 persons aged 18 years and older have a self-reported lifetime prevalence of epilepsy [13]. This study is the first to investigate the incidence of new onset seizures, epilepsy and seizure mimics in Ireland and, to our knowledge, the first to present epidemiological data on seizure mimics. We present our study protocol, adherent to I.L.A.E. and STROND guidelines, and findings for the first three months of data collection.

2.1.3 Materials and Methods

This study was carried out in the geographically defined area of Cork city and county over the course of the calendar year 2017, with an estimated total population of 542,868 persons based on a census in 2016. Herein we present our study protocol and, to demonstrate its application, the results of case ascertainment for the first three months of data collection, 1st January 2017 to 31st March 2017.

All acute medical hospitals were included with the exception of one solely private hospital that does not employ an on-site consultant neurologist. Acute seizures presenting to the medical assessment unit of that hospital are transferred to the tertiary university hospital in the city. The remaining 7 acute hospitals included in this study were as follows: 2 tertiary referral city center university hospitals, 2 regional secondary level hospitals, 1 solely private city center hospital which accepts acute referrals and employs 2 consultant neurologists, 2 city center hospitals with facilities for rehabilitation of geriatric patients who have recently been acutely admitted elsewhere e.g. ortho-geriatrics rehabilitation. This study also included community sources of case ascertainment as follows: all general practitioners (G.P.s) in Cork city and county who are registered with the Irish Medical Directory, all nursing homes and residential care centers registered with the Health Information and Quality Authority, and Epilepsy Ireland, the community based patient information and advocacy group.

2.1.3.1 Inclusion and exclusion criteria

We included all patients who had a suspected first seizure or new diagnosis of epilepsy from 1st January to 31st December 2017 whose registered address as per the hospital-based demographic information was within Cork city or county (defined area). The working diagnosis of 'seizure' had to be explicitly documented in medical correspondence during the patient's assessment

typically by a G.P. in the community, an emergency department triage nurse or physician, or senior hospital-based physician. Any patient, normally resident in the defined area, who had a suspected seizure during 2017 but presented to a hospital outside the area was included. These patients were identified through survey of G.P.s and neurologists in Cork city and county, where their ongoing care and follow up was based. All patients with an address outside of the defined area were excluded.

We gathered information on all patients whose first *presentation* to medical services with a query of seizure occurred during 2017. In some cases, the date of the first clinical event was prior to the 2017 calendar year, but medical attention was first sought in 2017, for example, when a patient has a history of recurrent stereotyped events, but the possibility of these events being seizures had not yet been explicitly stated, or medical attention was not sought. Similarly, we continued to monitor a number of case ascertainment sources [Rapid Access Seizure Clinic (R.A.S.C.) referrals, electroencephalogram (E.E.G.) and radiology databases] up to 31st March 2018 in order to complete the classification of patients who first *presented* in late 2017. By restricting our count to first presentation during 2017, we will avoid over- or under-ascertainment in the 2017 calendar year, and the number of first presentations classified will estimate the true incidence of each clinical subcategory.

As per the I.L.A.E. epidemiologic guidelines [4], febrile seizures in children (3 months to 6 years old) and neonatal seizures (<28 days old) were excluded from this study as they are felt to be separate from epilepsy *per se*. With regard to acute provoked seizures, we noted the incidence of their occurrence as a specific research question, but they were separated from epilepsy in the final analysis.

2.1.3.2 I.L.A.E. Definitions

- An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [1].
- Epilepsy is a disease of the brain defined by any of the following conditions: i) at least two unprovoked (or reflex) seizures occurring >24 hours apart ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or iii) diagnosis of an epilepsy syndrome [2].
- Acute provoked seizures are epileptic seizures which occur in close temporal association with an acute systemic, metabolic or toxic insult or in association with an acute central nervous system insult [4]. The interval between the insult and the seizure may vary according to the underlying clinical condition (see Table 2.1.1). With regard to alcohol withdrawal seizures, the seizure must have occurred within 7-48 hours of the last drink to be classified as an alcohol withdrawal seizure [14]. Alternatively, any patient with a history of alcohol abuse and acute provoked seizures from alcohol, who developed their first seizure independent from alcohol within the study period [and was therefore commenced on anti-epileptic drug (A.E.D)] was counted as a 'new diagnosis of epilepsy'. Seizures in the setting of acute alcohol intoxication due to extremely high quantities consumed and seizures in association with withdrawal of benzodiazepines were classified as acute provoked seizures [14].
- For all patients with a new diagnosis of epilepsy, the 2017 I.L.A.E. position papers on classification of seizures and epilepsy were applied. Seizures were therefore classified as focal onset, generalised onset or unknown onset and further descriptors were applied where possible [11]. Epilepsy was classified as focal, generalised, focal and generalised or unknown depending on available data [12].

2.1.3.3 Case ascertainment

We broadly divided our case ascertainment methods into 'hot pursuits', where information was gathered prospectively on a daily basis from active inpatient databases and services, and 'cold pursuits' where data were periodically reviewed retrospectively and cases were cross-referenced to the study database to prevent duplication. For an overview of the process of case ascertainment and case analysis, please see Figure 2.1.1.

2.1.3.3.1 'Hot pursuits'

i) Emergency departments. Triage recording systems vary in each of the hospitals and therefore it was necessary to screen emergency departments in different ways depending on the resources available. In the main university hospital of the city, electronic triage records allowed us to screen all patients presenting acutely to the emergency department and to identify all possible seizures. The electronic triage system was checked on a daily basis. Search terms including 'seizure', 'epilepsy', 'collapse', 'seizure-like events' and 'fits' were screened for among the initial post-triage electronic entries. The remaining hospitals operate paper based triage systems and a point of contact in each hospital was established to collect Medical Record Numbers (M.R.N.s) by hand of all patients presenting with a possible seizure.
ii) Radiology. The clinical indication for all CT and MRI brains performed in each of the included hospitals was reviewed systematically to capture all brain imaging requested for an indication of possible seizure. We included direct queries of 'first seizure' as well as more indirect queries such as 'collapse with jerking'.
iv) Inpatient services. Inpatient services with a high likelihood of assessing patients with first seizures were identified. These included neurology, geriatrics, oncology and neurosurgery inpatient services. These services were specifically targeted as it was felt that they might assess and treat patients for a possible seizure without necessarily ordering specific neurophysiology or neuroimaging

investigations. These teams were contacted on a fortnightly basis in order to prompt recall of recent cases.
v) Clinical Nurse Specialists (C.N.S.s). C.N.S.s from services felt to have a high likelihood of encountering patients with a first seizure were contacted on a monthly basis and asked to inform the study team of any new case. C.N.S.s in paediatrics, neurology and oncology participated in this study.

2.1.3.3.2 'Cold pursuits'

i) E.E.G. databases. There are three neurophysiology departments in the capture region, two public and one private. All paediatric and adult E.E.G. are performed at one of these three sites. The clinical indication for all E.E.G.s performed during the study period was reviewed and all possible first seizures and new diagnosis of epilepsy were included.
ii) R.A.S.C.. One consultant epileptologist works in the public service in the capture region (author D.C). This consultant runs a R.A.S.C. once per week with an aim of rapidly reviewing G.P. and emergency department referrals for 'query seizure'. All new referrals to this clinic were reviewed on a weekly basis.
iii) Survey of hospital consultants. Consultant physicians in neurology and geriatrics departments in the seven hospitals outlined above were contacted via postal survey every 8-12 weeks and asked to alert us if they were aware of any new case.
iv) Hospitals outside of the capture region. We acknowledge the possibility that a small proportion of patients whose residence is toward the outer edge of the capture region may present acutely to a regional hospital outside of the county. There are three acute hospitals in the neighboring counties with four consultant neurologists working between them. Each neurologist was contacted via a postal survey every 8-12 weeks and asked to alert us if they were aware of any new case which met our inclusion criteria.
v) General practice. All G.P.s in the defined region were contacted via postal survey every 12 weeks and asked to alert us if s/he was aware of any new case.

vi) Nursing Home and Residential Care survey. Clinical Nurse Managers of all registered nursing homes and residential care services were contacted via postal survey every six months and asked to alert us if s/he was aware of any new case. A six-month interval was chosen for nursing homes as case turnover is much lower than in general practice and we felt that recall would therefore be longer.
vii) Epilepsy Ireland. Epilepsy Ireland is a non-profit, nationwide patient advocacy and advice organisation for people with a diagnosis of epilepsy (www.epilepsyireland.ie). In order to rigorously identify any patient who may be resident in the defined area but who was diagnosed outside of one of the included hospitals, we contacted the local branch of Epilepsy Ireland. They reviewed their new patient database to identify patients who were ordinarily resident in the defined area but were diagnosed elsewhere. An Epilepsy Ireland staff member then consented the patient for inclusion in the study and forwarded their details to the study team.

Of note, we deliberately did not choose pharmacy data on A.E.D. prescribing or hospital coding databases for case ascertainment because in Ireland these databases are not linked to other medical data and typically do not discriminate between new cases and established cases of epilepsy.

2.1.3.3.3 Identifying under ascertainment

As a method of internal control, to determine if we were missing potential cases, we devised a method of assessment of case under ascertainment. We identified that patients with a known diagnosis of primary or secondary brain tumors are at increased risk of seizures [15]. We prospectively collected the M.R.N.s of patients discussed at the multidisciplinary neuro-oncology meeting of one tertiary referral university hospital from January to March 2017. Six months later, at the end of September 2017, we searched the medical records of these patients to identify if any had presented with a seizure. For any patient who had a seizure, we then crossed referenced them to our main database to see if they had already been captured through another method of ascertainment.

2.1.3.4 Case analysis

The paper medical record of each patient identified through the above methods was obtained from the medical records department. The first author (E.M.) abstracted the demographic details, clinical admission details and results of all relevant investigations of each case through medical chart review. For any patient who was reviewed and diagnosed by a consultant neurologist, we adhered to the final diagnosis of the consultant neurologist. For all patients who were not reviewed by a consultant neurologist, the case was analysed by E.M and D.C. and a consensus decision was made. Any patient without a clear consensus was further analysed at panel review with a second consultant epileptologist (E.C.). D.C. and E.C. are trained neurologists who completed epilepsy fellowships and have more than 9 years clinical experience running epilepsy services.

2.1.3.5 Case classification

Following record review, patients were classified as one of the following five categories; first provoked seizure, first single unprovoked seizure, new diagnosis of epilepsy, seizure mimic or indeterminate event (see Figure 2.1.1). Individuals with a first single unprovoked seizure were classified as new diagnosis of epilepsy when it was estimated that there was a greater than 60% chance of a recurrent epileptic seizure in the next 10 years, as per the I.L.A.E. operational definition of epilepsy [2]. Otherwise, they remained classed as first unprovoked seizure. For definite new cases of epilepsy, the seizure and epilepsy type were subclassified as focal, generalized or unknown according to the I.L.A.E. 2017 classification system [3]. Cases were classified as indeterminate, following discussion panel review, if there was insufficient clinical information to accurately classify the case.

The 2011 I.L.A.E. Epidemiology Commission report on standards for epidemiologic studies and surveillance of epilepsy [4] provides a classification system for the level of evidence available to support a diagnosis of an epileptic

seizure, or new diagnosis of epilepsy, based on the level of epidemiologic evidence available. Based on these standards, the following classification regarding level of evidence of both single epileptic seizures and new diagnosis of epilepsy were applied:

i) Definite: with primary documentation of (a) epileptic seizures, with evidence that these were unprovoked by any acute medical condition or transient brain disorder or (b) documentation of diagnosis by someone with appropriate specialised training in the recognition of epilepsy. Clear evidence of epileptic seizures was most often based on documented collateral history or documented history by medical staff in the case on inpatient events. In the event of a single documented seizure, evidence of an approximate 60% risk of recurrence was determined based on the presence or absence of risk factors for recurrence such as epileptiform abnormality on E.E.G. or significant brain imaging abnormality [16-19].

ii) Probable: with other sources of information indicating the likelihood that criterion (a) or (b) above is met. For example, cases were defined as probable where there was a history strongly suggestive of an epileptic seizure, but a witnessed history was not recorded.

iii) Possible: where primary or other sources of information suggest a possibility of epilepsy but neither (a) or (b) above is met. Possible epileptic seizures were defined as an event of which an epileptic seizure was one of a number of plausible differential diagnoses, but of which it was not possible to determine which was the most likely.

2.1.3.6 Accuracy of case information and classification

In order to ensure the data obtained from the medical records on each case was accurate and consistent, an internal audit of the data extraction was performed (by E.C.). Thirty-eight items were recorded from three randomly selected charts. Out of these 114 items (3x38), three items were discordant between E.C. and E.M. data extraction, resulting in a 97.4% concordance. None of the three discordant items altered the clinical diagnosis.

In order to ensure reliability of case classification, ten randomly selected cases were reviewed (by E.C). In the final classification, nine of the ten cases were in concordance. However, the internal audit highlighted the subjectivity of the I.L.A.E. practical diagnosis of epilepsy guidelines. In discussion, six of the 10 cases did not undoubtedly meet this criterion, and while all team neurologists agreed that these patients would be commenced on an A.E.D. due to risk of further seizures, whether this risk reached the 60% threshold was open to debate.

2.1.4 Results

The above protocol was applied to our study population from 1st January to 31st March 2018 in order to capture all patients who presented to medical services with a suspected first seizure or new diagnosis of epilepsy during the calendar year 2017. To demonstrate the protocol application, we present the results of the first three months of case ascertainment, 1st January 2017 to 31st March 2017.

A flow diagram of the potential cases of first seizure or newly diagnosed epilepsy from January 1st 2017 to March 31st 2017 is shown in Figure 2.1.2. Four hundred and forty two cases were initially identified. Following review of patient charts, 159 (40%) were excluded as they did not meet the inclusion criteria. The most common reason for exclusion was previously diagnosed epilepsy (n=69, 16%) or recurrent provoked seizures (n=25, 6%). Two hundred and eighty-three patients were included and were distributed between 6 of the 7 hospitals in Cork city and county.

A pie chart illustrating the overlapping hospital-based sources of case ascertainment is shown in Figure 2.1.3. Of the 283 included cases, fifty-five percent (n=156) were identified by a single source of case ascertainment, 27% (n=76) were identified by two sources, 11% (n=31) by three sources and 7% (n=20) were identified by more than three sources of ascertainment. No single

case was identified by all of the methods of case ascertainment. Regarding the contribution of individual sources of case ascertainment, almost 54% of cases were identified by reviewing radiology databases, see Table 2.1.2. The highest number of cases that was 'unique to source', meaning not identified elsewhere, came from review of E.E.G. databases.

Figure 2.1.4 illustrates the first round of postal surveys of G.P.s in the defined area. The response rate was 59%. Six G.P.s wrote back to indicate that they were retired and were therefore excluded from future surveys. Twenty-four potential cases were identified through this postal survey; however 8 were subsequently excluded as they did not meet the inclusion criteria. Sixteen cases were included in the study, none of which was unique to the G.P. survey in terms of source of case ascertainment. The community based patient advocacy group Epilepsy Ireland reviewed their records and did not yield any new cases diagnosed outside of a Cork hospital in the first three months of cases ascertainment.

Figure 2.1.5 illustrates the break-down of identified patients into each of the five subclassifications- first provoked seizure, first unprovoked seizure, new diagnosis of epilepsy, seizure mimics and indeterminate. Among the 95 cases of new diagnosis of epilepsy, 75 (79%) were patients who had a first seizure in 2017, and had an estimated greater than 60% chance of further seizures, therefore met the criteria for a practical definition of epilepsy [2]. Seventy-one of the new diagnosis of epilepsy were considered definite, and of these 71% (n=50) were focal, 18% (n=13) were generalized and in 11% (n=8) cases it was unknown whether epilepsy was focal or generalized according to the I.L.A.E. 2017 subclassification of seizure and epilepsy type. Seizure mimics represented the largest group (n=113, 40% of all reviewed case records) and the most commonly encountered seizure mimic was syncope (40%, n=45). There were 10 (3%) indeterminate cases in the first three months of data collection. Extrapolating the first three months of data, the crude incidence for new diagnosis of epilepsy in our population was 59 per 100,000 people per year, however it is necessary to highlight that this is an estimated rate which is likely to increase as it does not allow for 'late entries' due to lag in case ascertainment

methods. The incidence is higher than previous studies outlined in Table 2.1.3 and therefore reinforces the importance of multiple methods of case ascertainment.

To estimate potential case under-ascertainment, 63 patients were identified by screening three months of multidisciplinary neuro-oncology meetings at a tertiary referral center. Of these, 5 had a previous diagnosis of epilepsy and 36 were not resident in the defined area therefore were not eligible for inclusion in the study. The medical charts of the remaining 22 patients were reviewed and none had a documented seizure during follow-up.

2.1.5 Discussion

We present an epidemiological protocol that adheres to recently published international guidelines for investigation of the incidence of epilepsy within a population [4,10]. Furthermore, we have incorporated recently updated I.L.A.E. guidelines for the clinical classification of seizures and epilepsy [11,12] which have not yet been used in epidemiological studies but which will be of increasing importance in international epilepsy research. Our case ascertainment protocol is rigorous and, when data analysis is complete, will be the first to report the incidence of epilepsy, first unprovoked seizures and first provoked seizures in Ireland. Finally, to our knowledge, this will be the first study to additionally report the incidence and characteristics of 'seizure mimics' within the same population that seizures and epilepsy are under study. Inclusion of the related diagnosis of first seizures, epilepsy and seizure mimics in our study protocol gives a sense of the scale of this cohort and the significant impact on healthcare services investigating and treating these patients. Further details on age-adjusted incidence , seizure and epilepsy etiology, and classification will be reported separately when annual incidence data is complete.

Many previous epidemiologic studies have focused on a specific cohort within a population, for example children or the elderly. Relatively few have included all age-groups and, within those studies, all available case ascertainment methods

range from use of a single source to multiple overlapping sources, see Table 2.1.3. With regard to case ascertainment in our study, we aimed for full capture of new events by combining as many methods of ascertainment as was practicable in our population. As shown in Table 2.1.3, the majority of other studies do not use such an extensive combination of methods. For example, Jallon et al., 1997 [20] used E.E.G. database as the sole method of case ascertainment. In our study, E.E.G. databases identified only 53% of cases. Furthermore, our interim three-month analysis demonstrates the importance of including all possible methods of ascertainment as no single case was picked up in every method. In addition, we specifically targeted inpatient teams and C.N.S.s with a high likelihood of encountering a patient with a first seizure, for example, the neurosurgical and oncology teams, and contacted them on a regular basis to maximize case ascertainment. These methods identified 10 'unique to source' cases, not identified by other methods in the first three months of case ascertainment. To our knowledge, this is the first study to apply such a method.

The seminal work by Hauser and Kurland, 1975 [21] in Rochester Minnesota demonstrates the usefulness of accurate medical record databases to perform epidemiologic studies. However, such medical record linkage systems are not available in many countries, including Ireland, and therefore in order to obtain accurate epidemiologic data overlapping methods of case ascertainment are required. Data obtained from cohort specific databases were used by Annegers et al., 1999 [22] to describe the incidence of epilepsy in a multiethnic urban population (35.5 per 100,000). However, this database contained information only on those enrolled in a health maintenance organization served by a particular clinic and was therefore findings may not be generalizable to the whole population as the clinic served only people in employment and their dependents. Correspondingly, this study demonstrated low incidence among those over 65 years of age, in contrast to most other studies. Therefore, in populations where accurate, whole population, medical record databases are not in existence, multiple over lapping methods of ascertainment, in combination with medical chart review, as demonstrated by our study, provide detailed information for case identification, classification and determination of etiology.

An early study in Italy [25] was unique in its use of social workers and teachers in the community to maximize case ascertainment, see Table 2.1.3. However, due to ethical and practical considerations this would no longer be a viable source of case ascertainment. Finally, studies carried out in lower income countries, with less well developed health resources, have used door-to-door community surveys to ascertain cases, for example [26,27]. However, this method is vulnerable to under-ascertainment if stigma is associated with epilepsy and seizures in the population. Furthermore, accuracy of diagnosis and classification of cases is difficult when this method is used in isolation. Therefore, when adequate health resources permit, such as in our study, the use of hospital-based databases to identify and classify patients based on clinical information is preferable.

Other potential sources of case ascertainment were also considered. Previously published studies investigating adult populations have used A.E.D. prescription databases as a source of case ascertainment [23, 24]. However, it was not possible to use A.E.D. prescribing databases in our case ascertainment for a number of reasons. Firstly, drug prescribing data are not linked to other patient records in our population, therefore it would not have been possible to cross reference such information to our database. Secondly, patients presenting with a first seizure or seizure mimic may not routinely be prescribed an A.E.D. and therefore would not be captured by such a method. Thirdly, A.E.D.s are often used for indications other than epilepsy, such as neuropathic pain, and therefore may overestimate the diagnosis of epilepsy. Finally, use of a drug prescription database over the course of a year, without linkage to other patient records, would not give an accurate account of patients who were *newly* prescribed the medication. Therefore, in our population, such a method would be more appropriately applied to estimating prevalence of epilepsy rather than incidence, as was demonstrated by Linehan et al., in 2010 [13].

Very few studies address under-ascertainment. MacDonald et al., 2000 [28] cross-referenced general practice databases with local hospital patient

administration system to try to ensure complete ascertainment. However, this method relies on accurate and complete case coding. For a number of patients, a seizure may not be the primary reason for attending hospital, for example, patients incorrectly initially diagnosed as a stroke, or patients who have their first seizure while medically unwell for another reason. To our knowledge, our study is the first to design a unique method of following 'at risk' patients as a method of assessment of under-ascertainment. However, for the first three months of data collection, none of these at risk patients proceeded to have a seizure. We propose to follow this cohort for a longer time-frame in order to determine under-ascertainment and validate this unique method. On the other hand, it is reassuring that no community obtained case (from general practice or nursing homes) had not been identified already using the hospital-based methods, and therefore this serves as somewhat of a surrogate of complete ascertainment.

Our study highlighted the subjectivity involved in determining whether, following a single seizure, a person is at greater than 60% risk of further seizures, as found by our panel discussion. The Multicenter Trial for Early Epilepsy and Single Seizures (M.E.S.S.) [29] provides some guidance on assessing this risk. However, the M.E.S.S. study did not include neuroimaging as part of its risk stratification tool and there remains a lack of up-to-date, real world clinical data in certain populations, for example, older adults with established small vessel ischaemic disease with juxtacortical signal changes on brain imaging. In clinical practice, many patients commence an A.E.D. because they are considered at some risk of recurrent events, even though the exact risk is unquantifiable. The 2014 I.L.A.E. practical definition of epilepsy does not require the clinician to quantify the risk precisely. Therefore, we have included patients within the cohort of new diagnosis of epilepsy who were determined to be at an approximate 60% risk of recurrent seizures based on the evidence available to date. Further study of individuals at the margin of this risk threshold is required.

We are aware of potential gaps in case ascertainment, for example people who did not seek medical help after a seizure, people who do not recognize that they

have had a seizure(s) and vulnerable patients unable to access medical care including homeless people, non-verbal individuals and people living alone. In addition, epilepsy and mimics largely are based on clinical history. In a small number of cases the treating physician may not recognize seizure as a potential diagnosis. However, through our study design, we have maximized case ascertainment in as much as possible.

2.1.6 Statements

2.1.6.1 Acknowledgement

The authors would like to thank all hospital-based medical, nursing, neurophysiology, radiology and medical records administrative staff as well as community-based G.P.s and nursing home staff who contributed and responded to the study. We would also like to thank Dr. Paul Corcoran (School of Public Health, University College Cork) and Dr. Carol Sinnott for advice during study design.

2.1.6.2 Statement of Ethics

Ethical approval was obtained from the Clinical Research Ethics Committee (C.R.E.C.) of the Cork Teaching Hospitals (Appendix 1). This was an observational study and following collection, all data were anonymized and stored on a password-protected computer in the Department of Neurology, Cork University Hospital.

2.1.6.3 Disclosure Statement

The authors have no conflicts of interest to declare.

2.1.6.4 Funding sources

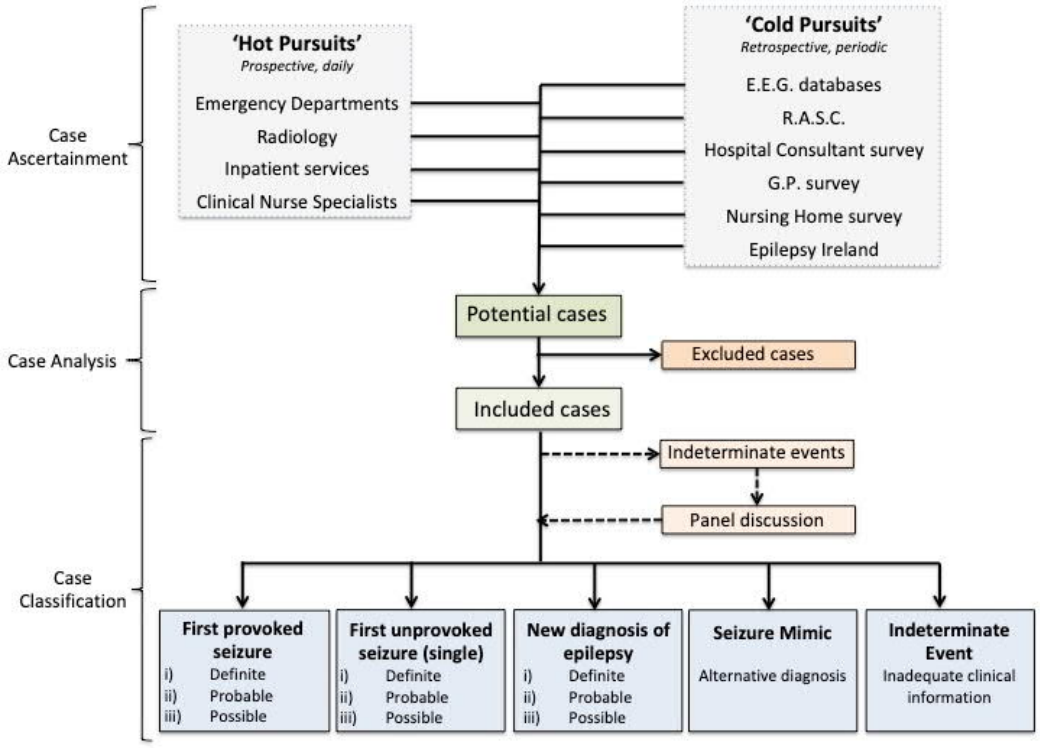
No specific funding was received by any author with regard to this study.

2.1.6.5 Author Contributions

E. Maloney was involved in study design, data collection, data analysis and manuscript preparation. E. Chaila was involved in study design, data analysis and manuscript preparation. É. O'Reilly was involved in study design, data analysis and manuscript preparation. D. Costello was involved in study design, data collection, analysis and manuscript preparation.

2.1.7 Figures

Figure 2.1.1 Overview of case ascertainment, case analysis and case classification protocol.[6]



[6] E.E.G.= Electroencephalogram; G.P.= General Practitioner; R.A.S.C.=Rapid Access Seizure Clinic

Figure 2.1.2 Flow diagram of identification of potential cases of first seizure and newly diagnosed epilepsy in the capture region over the study period 1st January to 31st March 2017.

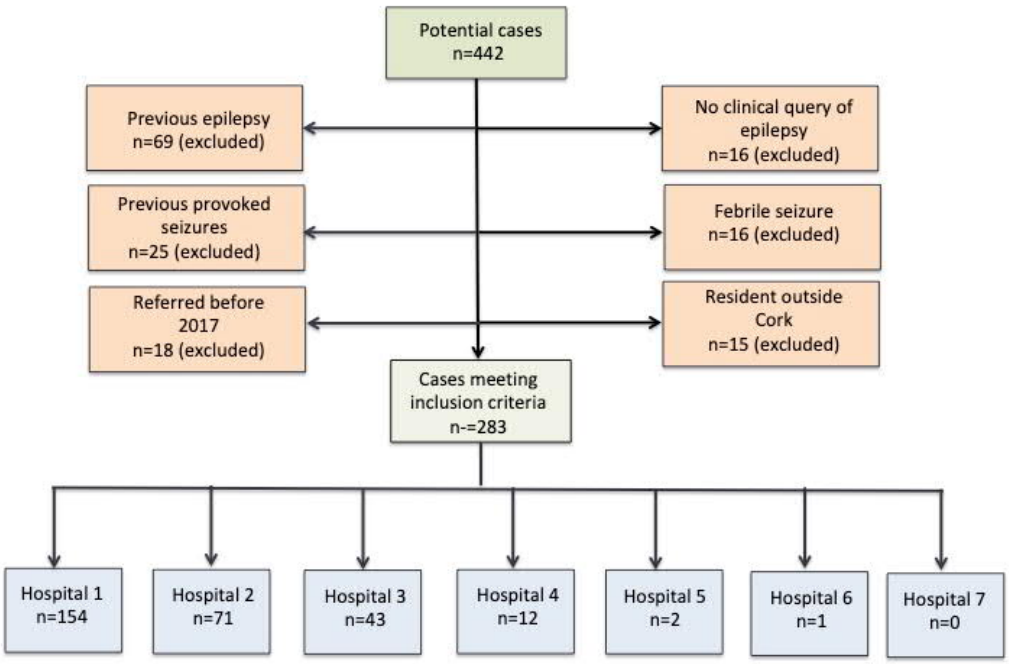
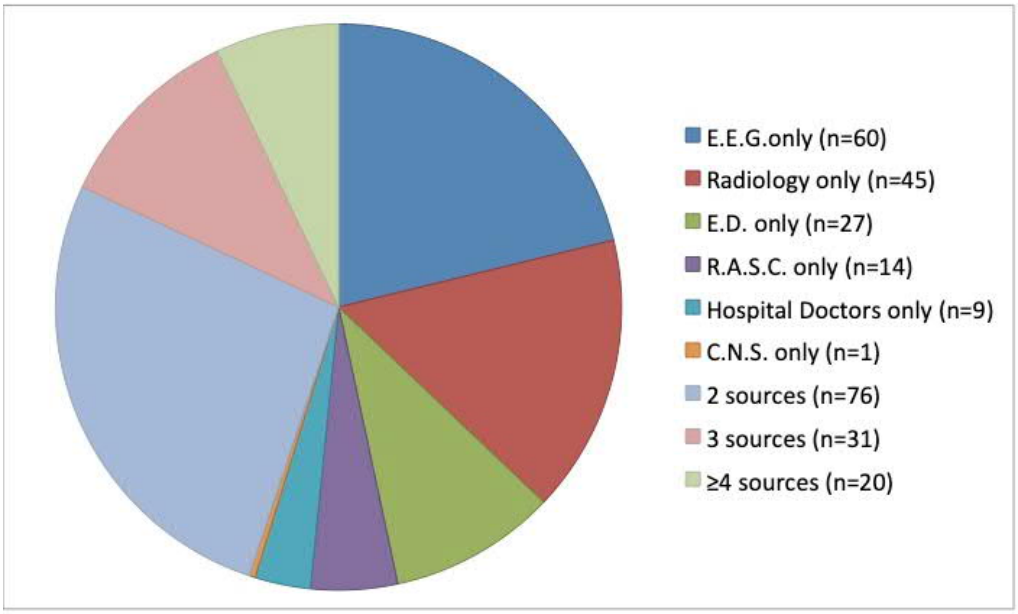


Figure 2.1.3 Pie chart demonstrating overlapping sources of hospital based case ascertainment during study period 1st January to 31st March 2017.

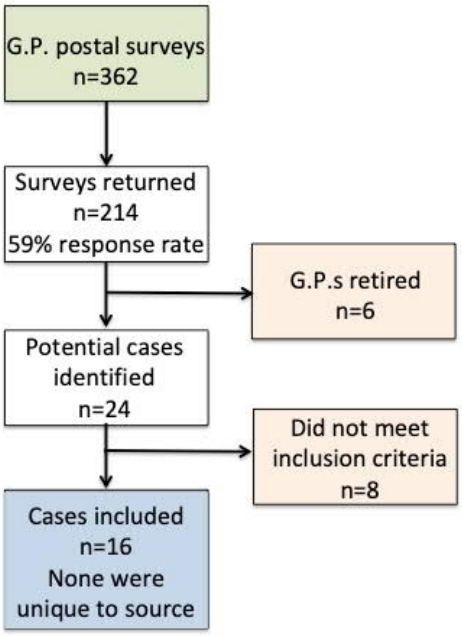
The chart shows the proportion of included cases identified uniquely by each of the six hospital based methods as well as the proportion of cases identified by 2, 3 or more than 3 individual sources (n=283).[7]



[7] C.N.S.= Clinical Nurse Specialist, E.D.= Emergency Department, E.E.G.= electroencephalogram, R.A.S.C.= Rapid Access Seizure Clinic.

Figure 2.1.4 Flow diagram illustrating case ascertainment by postal survey of all G.P.s in the capture region during study period 1st January to 31st March 2017.

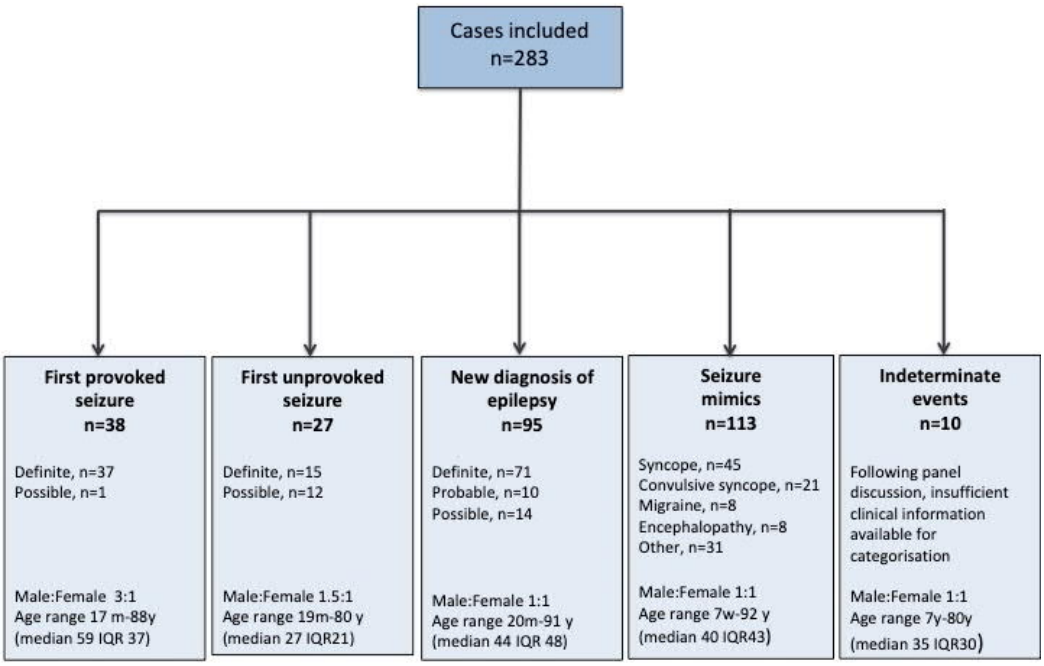
A total of 16 cases were included from this method of ascertainment, all of whom had been previously identified through hospital based ascertainment.[8]



[8] G.P.= General Practitioner

Figure 2.1.5 Number of cases in each subgroup following panel review of case information.

Of the 95 cases of new diagnosis of epilepsy, 75 also presented with their first seizure and were determined to be at greater than 60% risk of recurrent seizures.[9]



[9] IQR= interquartile range, m=months, w=weeks, y=years.

2.1.8 Tables

Table 2.1.1 Examples of provoked seizures in association with disruption of the structural or functional integrity of the brain.

Adapted from the I.L.A.E. Standards for Epidemiologic Studies [4]

Cause [14]	Period of occurence	Notes/exceptions
Cerebrovascular disease [26-28]	First 7 days	
Traumatic brain injury [28,29]	First 7 days	Included intracranial surgery. Longer intervals are acceptable for subdural haematoma in the absence of known trauma or at first identification of haematoma. Subsequent seizures are unprovoked.
CNS infection [28]	First 7 days	Included seizures occuring after 7 days in patients with persistent clinical and/or laboratory signs of infection.
Cerebral tuberculoma [14]	During treatment	Seizures occuring after successful treatment are unprovoked
Brain abscess [14]	During treatment	Seizures occuring after successful treatment are unprovoked
HIV infection [14]	Acute infection or severe metabolic disturbance	Seizures occuring in the absence of oppotunistic CNS infection or severe metabolic disturbance are unprovoked
Arterovenous malformation [14]	In the presence of acute haemorrhage	All other seizures are unprovoked
Multiple sclerosis [14]	First presenting symptom within 7 days of relapse	
Autoimmune disease [14]	Signs or symptoms of activation	

Table 2.1.2 Cases identified at each source expressed to the nearest percentage.[10]

All included potential first seizure or new diagnosis epilepsy patients (n=283)		
Source	Number of cases (%)	Unique to source (%)
Radiology	153 (54%)	45 (16%)
E.E.G.	151 (53%)	60 (21%)
Emergency department	70 (25%)	27 (9%)
Hospital Doctors	53 (19%)	9 (3%)
R.A.S.C.	45 (16%)	14 (5%)
Community survey	16 (6%)	0 (0%)
C.N.S.	11 (4%)	1 (<1%)
Epilepsy Ireland	0 (0%)	0 (0%)

[10] R.A.S.C.= Rapid access seizure clinic; C.N.S.= Clinical nurse specialist

Table 2.1.3 Comparison of case ascertainment methods in previous studies investigating the incidence of epilepsy and/or first seizures within a population

Studies included all age groups within the population studied. [11]

Study	Current study	Olafsson et al., 2005 [34]	MacDonald et al., 2000 [28]	Jallon et al., 1999 [35]	Jallon et al., 1997 [20]	Loiseau et al., 1990 [9]	Joensen 1986 [36]	Granieri et al., 1983 [25]	Hauser and Kurland, 1975 [21]	De Graaf 1974 [37]
Geographic area (population)	Cork, Ireland, (542, 868)	Iceland, (882, 151)	London, United Kingdom, (100,230)	Martinique Island (383,596)	Genevea, Switzerland (384,657)	Southwest France (1,128,164)	Faroe Island (41,144)	Copparo, Italy (45,153)	Rochester, United States	Northern Norway (215,000)
Case ascertainment										
Radiology database	X	X								
E.E.G. database	X	X			X	X	X	X		X
Emergency Department	X	X		X						
Neurologists/Paediatricians	X	X		X		X		X		
Other hospital specialists	X	X								
R.A.S.C.	X		X							
Clinical Nurse Specialist	X									
G.P. survey	X	X	X	X			X	X		
Residential care survey	X	X								
Patient Advocacy Group	X									
Hospital medical record data			X					X	X	X
School teachers and social workers								X		
Incidence of first unprovoked seizures (per 100,000)		56.8	11	64.1	45.6	71.3 (all seizures)			23.6 (all seizures)	
Incidence of first provoked seizures (per 100,000)				16.4	25.2					
Incidence of epilepsy (per 100,000)		33.3	46				42.8	33.1	48.7	32.8

[11] E.E.G.= electroencephalogram. R.A.S.C= Rapid Access Seizure Clinic. G.P.= General practitioner.

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2.2 Completion of data collection (1st January 2017-31st March 2018)

2.2.1 Continued surveillance of case ascertainment

As outlined in Section 2.1.3.1, certain methods of case ascertainment continued until 31st March 2018 in order to capture late entries, i.e. cases who may have presented in 2017, but who did not have had investigations until 2018. As such, inpatient services were contacted up to 7th January 2018, E.D. triage systems were monitored until 14th January 2018, at which point it was clear that no new cases were being ascertained. C.T. imaging, which is usually used in the acute setting, was screened until 31st January 2018. M.R.I. imaging, E.E.G., and R.A.S.C., which have a longer waiting list and are often outpatient tests, were screened up to 31st March 2018. The final ascertainment survey to hospital consultants in surrounding counties, G.P.s and nursing homes was sent on 8th January 2018. A final check for cases with Epilepsy Ireland was sent on 15th January 2018. Tables 2.2.1, 2.2.2 and 2.2.3 demonstrate results on completed case ascertainment for the entire study period. Figures 2.2.1 and 2.2.2 demonstrate response rates and results from community ascertainment methods.

2.2.2 Figures

Figure 2.2.1 Response rate and case ascertainment from postal survey of nursing homes and residential care units for entire study period.

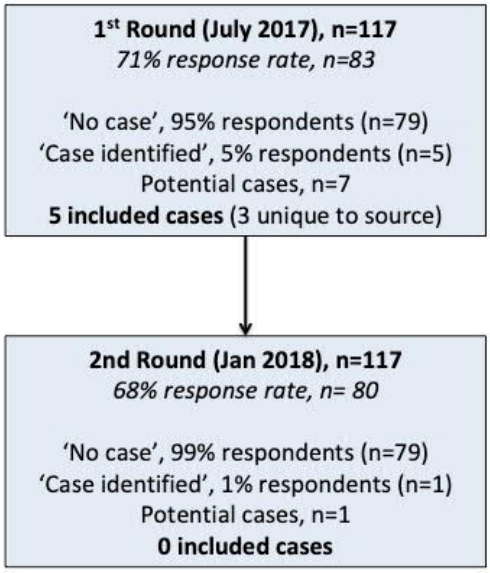
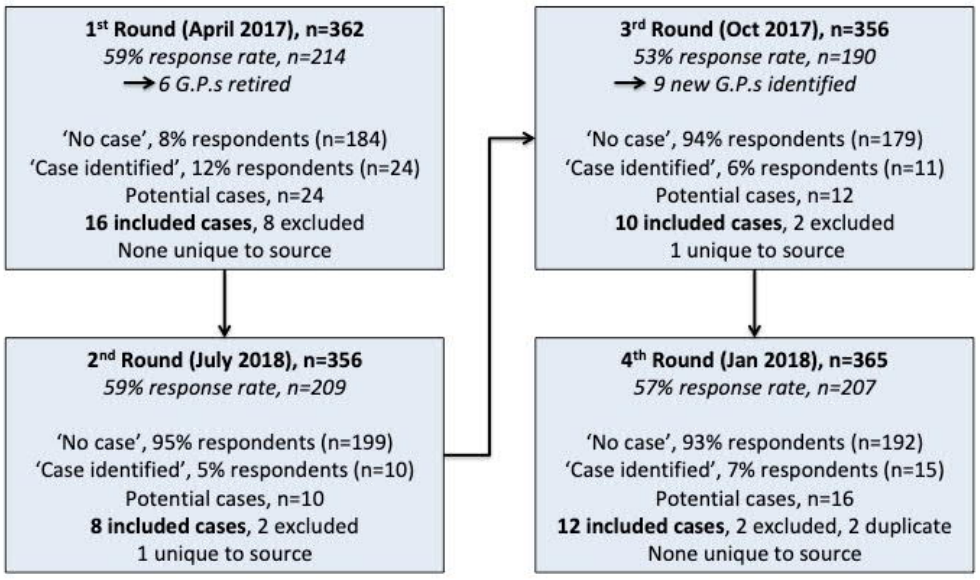


Figure 2.2.2 Response rate and case ascertainment from postal survey of G.P.s for entire study period.[12]



[12] G.P.= General Practitioner

2.2.3 Tables

Table 2.2.1 Number of cases identified at each hospital site over entire study period

Total cases included, n=1330. Note: thirty three cases were identified at more than one hospital.

Hospital	Cases ascertained
Cork University Hospital (CUH)	802 (60%)
Mercy University Hospital	265 (20%)
Bon Secours Hospital	176 (13%)
Bantry General Hospital	57 (4%)
CUH Private Clinic	21 (2%)
Mallow General Hospital	15 (1%)
Cork University Maternity Hospital	8 (<1%)
St. Finbarr's Hospital	5 (<1%)
University Hospital Kerry	5 (<1%)
Other	5 (<1%)
South Tipperary General Hospital	4 (<1%)
More than one hospital	*33 (2%)*

Table 2.2.2 Cases identified at each source expressed to the nearest percentage over entire study period.[13]

All included potential first seizure or new diagnosis epilepsy patients (n=1330)		
Source	Number of cases (%)	Unique to source (%)
E.E.G.	748 (56%)	302 (23%)
Radiology	708 (53%)	207 (16%)
Emergency departments	353 (27%)	115 (9%)
R.A.S.C.	155 (12%)	48 (4%)
Non Consultant Hospital Doctors	137 (10%)	23 (2%)
Consultant Physicians	117 (9%)	17 (1%)
Clinical nurse specialist	65 (5%)	5 (<1%)
Community survey	51 (4%)	5 (<1%)

Table 2.2.3 Number of cases identified by overlapping methods of case ascertainment over entire study period.

(total cases, n=1330).

Number of methods of ascertainment	Number of cases
1	722 (54%)
2	340 (25%)
3	168 (13%)
4	74 (5%)
5	23 (2%)
6	3 (<1%)
7	0
8	0

[13] E.E.G.= electroencephalogram, R.A.S.C.= Rapid Access Seizure Clinic.

Chapter 3 The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in a defined geographic area

This chapter of my PhD thesis was accepted for publication in *Neurology* in January 2020 (final publication Neurology 2020; Aug 4;95(5):e576-e590). This paper presents the main study findings with regard to crude and age-adjusted incidence of first seizures, new diagnosis of epilepsy and seizure mimics in the defined geographic area of Cork city and county during the calendar year 2017. In addition, the implications of the 2014 updated I.L.A.E definition of epilepsy are demonstrated and discussed. Co-authors on the submitted manuscript are Dr. Elijah Chaila, Dr. Éilis O'Reilly and Dr. Daniel Costello.

3.1 Abstract

Objective: To determine the incidence of first seizures, epilepsy and seizure mimics in a geographically defined area using the updated 2014 International League Against Epilepsy (I.L.A.E.) definition which allows an epilepsy diagnosis following a single seizure where risk of further seizures over the next 10 years is approximately 60% or more. This replaced the 1993 definition where epilepsy was diagnosed when a person had two or more seizures separated by 24 hours.
Methods: Using multiple overlapping methods of case ascertainment followed by individual case classification by an epileptologist we identified all first seizures, new diagnosis of epilepsy, and seizure mimics occurring in a defined geographic area (population 542,868) 01/01/2017-12/31/2017. Incidence was age-standardised to the Standard European Population. We compared incidence rates when using the 2014 and 1993 I.L.A.E. definitions.
ResuIts: When applying the 2014 I.L.A.E. definition of epilepsy the incidence of new diagnosis of epilepsy was 62 per 100,000 (age-standardised 74), compared to 41 per 100,000 (age-standardised 48) when applying the 1993 definition, and the difference was more pronounced at older ages. The incidence of all first seizures and of seizure mimics was 102 per 100,000 (age-standardised 123) and 94 per 100,000 (age-standardised 111), respectively. The most frequently encountered seizure mimic was syncope.
Conclusion. Application of the 2014 I.L.A.E. definition of epilepsy resulted in higher incidence of new diagnosis of epilepsy compared to the 1993 definition. The incidence of seizure mimics almost equals that of all first seizures. Seizures, epilepsy and seizure mimics represent a significant burden to healthcare systems.

3.2 Introduction

Epilepsy is a notable cause of disability and mortality[1] and poses a substantial economic burden for health care systems, individuals and their families.[2] Detailed reporting of incidence studies of epilepsy has been called for to address gaps in knowledge of incidence of seizures and epilepsy by age, seizure type and aetiology.[1, 3] Expert assessment of patients presenting with first seizures is critical to differentiating epileptic seizures from other conditions that resemble epileptic seizures ('seizure mimics'). Although first seizures and epilepsy are susceptible to misdiagnosis, to our knowledge there are no published incidence studies on seizure mimics.

A recent meta-analysis of 13 studies estimated that the incidence rate of epilepsy was 61.44 per 100,000 persons-years (95%CI 50.75-74.38).[3] However, there was significant heterogeneity of the estimate between studies, with reported incidence rates ranging from 33.9 to 215 per 100,000 person-years. Possible explanations for such differences may be country-level income, case ascertainment methods or differing definitions of epilepsy. In an effort to promote consistency in methods used in epidemiologic studies and to facilitate comparisons between populations, the International League Against Epilepsy (I.L.A.E.) has proposed standards for epidemiologic studies and surveillance of epilepsy.[4]

Previously, in both epidemiologic studies and clinical practice, the diagnosis of epilepsy required two or more unprovoked seizures occurring at least 24 hours apart.[5] In 2014, the I.L.A.E. updated its operational definition of epilepsy,[6] such that a person can now be diagnosed with epilepsy following a single unprovoked seizure if it is estimated that he or she has an approximate 60% or greater risk of recurrent seizures over the next ten years. In 2017, Aaberg et al.[7] reported a 3% higher incidence of epilepsy when the 2014 definition was applied to a cohort of children aged up to ten years compared to the 1993 definition.[5] To our knowledge, this updated operational definition has not yet been incorporated into any whole population epidemiologic study of epilepsy.

3.3 Methods

3.3.1 Base population

This study was carried out in the geographically defined area of Cork city and county, Ireland, with an estimated population of 542,868, predominantly Caucasian (93%), adults and children based on national census data from 2016.[8] The area contains one large urban development which encompasses approximately one quarter of the total population (125,657 adults and children). The remaining population lives in smaller towns, villages or rural dwellings. The geographic area spans approximately 7,500 km^2. We report our results in adherence with S.T.R.O.N.D. guidelines.[9]

3.3.2 Case ascertainment and classification

A detailed description of the epidemiologic protocol applied to this population has been previously published.[10] In brief, multiple over-lapping sources of case ascertainment were applied to the geographically defined area from 1st January 2017 to 31st March 2018 in order to capture all cases of possible first seizure, new diagnosis of epilepsy and seizure mimics whose first interaction with medical services for the event occurred during the calendar year 2017. Case ascertainment relied on a combination of prospective and retrospective methods in both community and hospital settings, see Figure 3.1. All patients who presented to medical services during the calendar year 2017 with a possible first seizure or new diagnosis of epilepsy whose address, as per the hospital based administrative system, was within the geographically defined area were included. In accordance with the I.L.A.E. epidemiologic guidelines,[4] neonatal seizures and febrile seizures were excluded. Cases with inadequate or unclear documentation were classified as indeterminate. Epileptic seizures and epilepsy were defined according to the I.L.A.E. operational definitions.[6, 11] Epilepsy type was classified as focal, generalised or unknown according to the 2017 I.L.A.E.

Commission report.[12] Provoked seizures[13] were identified as a specific sub-cohort, and were separated from first unprovoked seizures and epilepsy.

Following the identification of a potential case, the medical-chart and investigations of the patient were reviewed first-hand. In accordance with the I.L.A.E. epidemiologic study guidelines,[4] the probability that an event was a seizure was defined as either a definite, probable or possible based on the evidence available, as follows:
i) Definite: with primary documentation of (a) epileptic seizures, with evidence that these were unprovoked by any acute medical condition or transient brain disorder or (b) documentation of diagnosis by someone with appropriate specialised training in the recognition of seizures/epilepsy. Clear evidence of epileptic seizures was most often based on documented collateral history or documented history by medical staff in the case on inpatient events.
ii) Probable: with other sources of information indicating the likelihood that criterion (a) or (b) above is met. Cases were defined as probable where the clinical history was strongly suggestive of an epileptic seizure, but a witness history was not recorded, for example a patient found alone in collapsed unresponsive state with seizure markers such as tongue biting.
iii) Possible: where primary or other sources of information suggest a possibility of epilepsy but neither (a) or (b) above is met. Possible epileptic seizures were defined as an event of which an epileptic seizure was one of a number of plausible differential diagnoses, but of which it was not possible to determine which was the most likely.

Patients who initially had a working diagnosis of epileptic seizure as judged by a first-line decision-maker [for example, an emergency department physician, general practitioner (G.P.)], but who were ultimately determined not to have had a seizure (by an epileptologist, senior neurologist or senior physician), were classified as ‘seizure mimics’. Based on the evidence available from chart review, investigations and assessment by the treating physician, a specific alternate diagnosis to a seizure was specified where possible. Patients who were

determined not to have had a seizure, but in whom it was not possible to assign a specific diagnosis, were labelled as unclassified seizure mimics.

The 2014 I.L.A.E. operational definition of epilepsy[6] outlines that following a single unprovoked seizure a person with an estimated approximate 60% or greater risk of further seizures occurring over the next 10 years can be diagnosed with epilepsy. Definite, probable and possible single unprovoked seizures were classified as definite, probable or possible epilepsy, respectively, if one or more of the following risk factors were identified: persons with a structural or remote symptomatic aetiology and/or epileptiform abnormality on electroencephalogram (E.E.G.)[14-16] adults with a significant structural brain imaging abnormality,[15, 17, 18] neurodegenerative dementia,[19] or extensive small vessel disease with juxtacortical lesions.[20] Central to the quantification of risk was a clinical judgement by an experienced epileptologist (D.C. and E.C.) on how likely was a patient to have further seizure(s) over the next 10 years if not started on an anti-epileptic drug (A.E.D.). Patients with two or more seizures were also classified as having epilepsy. This classification was independent of whether the treating physician had commenced the patient on an A.E.D. Patients with mild-to-moderate small vessel disease without juxtacortical involvement, other non-specific findings or normal investigations were classified as a single unprovoked seizures.

As outlined previously,[10] we applied a novel method of assessment of case under-ascertainment to the defined area by prospectively following a cohort of patients determined to be at high risk of seizures.[21, 22] A neuro-oncology multidisciplinary meeting occurred twice a month in the tertiary level hospital to discuss cases from the hospital catchment area with a primary or secondary brain tumour. Patients identified at the multidisciplinary meeting from January 2017 to June 2017 were prospectively followed until 2018. Case notes were reviewed in March 2018 to determine if a patient had been diagnosed with a seizure or epilepsy during the calendar year 2017. If a new diagnosis of seizure or epilepsy had occurred, the patient was cross-referenced to our study database

to determine if they had been ascertained through one of the overlapping methods of case ascertainment.

3.3.3 Statistical analysis

Demographic data are presented as median and interquartile range (I.Q.R.). Only definite and probable cases of seizures and epilepsy were included in the calculation of incidence and analysis of aetiology. Demographic data from All Ireland Census 2016 [8] was used to calculate annual age-group and sex-specific incidence per 100,000 population. Ninety-five percent confidence intervals were calculated for annual incidence. Age-standardisation was performed by comparison to the 2013 European Standard Population.[23] Eurostat does not provide information on certain age groups, for example, those aged less than one. Therefore, for age standardisation 5-year age groups were used. Statistical analyses were performed using SPSS version 24 for Mac.

3.3.4 Standard protocol approvals

The study protocol was approved by the University College Cork Clinical Ethics Research Committee (Appendix 1). Following ascertainment, the data were anonymised prior to analysis and storage.

3.3.5 Data availability

Anonymized data can be shared by request from any qualified investigator.

3.4 Results

3.4.1 Case capture and inclusion

Figure 3.1 illustrates the study overview and the number of cases ascertained and classified in each of the four diagnostic categories of first provoked seizure, first unprovoked seizure, new diagnosis of epilepsy and seizure mimic. The most common reason for exclusion was an absence of a plausible clinical query of an epileptic seizure on chart review (n=194, 32% of excluded cases). For example, cases for whom an E.E.G. was ordered for a clinical query of rapidly progressive dementia. Eight patients had both a first provoked and a first unprovoked seizure during the study period. One patient presented with a first provoked seizure secondary to a haemorrhage from a cavernoma and was classified as epilepsy because brain imaging showed multiple other cerebral cavernomas thus the patient was judged to be at approximately 60% or greater risk of recurrent seizures.

Of the 1330 cases included, 54% (n=722) were identified by a single source and 46% (n=608) were identified by multiple sources. Out of up to 8 sources of case ascertainment, the maximum number of methods that any individual case was captured by was 6 (n=3). Review of E.E.G. databases provided the largest number of included cases (n=748, 56%) and the largest number of unique-to-source cases (n=302, 23%).

3.4.2 Incidence and classification

The sex- and age-group specific and total unadjusted and age- standardised incidence of all definite and probable first seizures, new diagnosis of epilepsy, and seizure mimics are presented in Table 3.1. The incidence was higher in males than females in all diagnostic groups with the exception of seizure mimics. The incidence of each diagnostic group was bimodal with highest incidences in those under one and over 65 years of age, see Figure 3.2.

Seventy-one percent (n=240) of definite and probable new diagnosis of epilepsy were classified as focal, 11% (n=37) were classified as generalised and 18% (n=59) had an unknown epilepsy type. Structural aetiology represented the most common aetiology of epilepsy (54%, n=182). Thirty percent (n=102) of definite and probable cases of epilepsy had an unknown aetiology. Twelve percent of cases (n=39) had a genetic aetiology as a cause of epilepsy, either genetic generalised epilepsy (9·5%, n=32) or gene specific disorders (2%, n=7).

In order to compare incidence with previous studies, we calculated the incidence of epilepsy in our population using the 1993 I.L.A.E. definition[5] (i.e. a history of two or more unprovoked seizures), see Table 3.2. Similar to the 2014 I.L.A.E. definition,[6] incidence displayed a bimodal age distribution, see Figure 3.3. The annual incidence increased when the 2014 definition[6] was applied as compared to the 1993 definition[5] in all age groups and this increase was greatest in older age groups. Ninety-one percent (n=307) of patients with a definite or probable diagnosis of epilepsy according to the 2014 definition[6] were prescribed an A.E.D. Ninety-three percent (n=206) of those with a definite or probable diagnosis of epilepsy according to the 1993 definition[5] were prescribed an A.E.D.

The incidence of seizure mimics was almost equal to the incidence of first seizures, see Figure 3.4 and Table 3.1. In older age groups, a diagnosis of first seizure became more likely than a diagnosis of seizure mimic. Vasovagal syncope and convulsive syncope constituted almost half of the seizure mimics (47%, n=238). Of patients who were admitted to the hospital for more than 24 hours, the median length of stay was 5 days (I.Q.R 9) for all first seizures (n=722) and 4 days (I.Q.R. 7) for all seizure mimics (n=510).

3.4.3 Assessment of under ascertainment

In March 2018, we reviewed the medical notes of 155 patients discussed at the neuro-oncology meeting from January to June 2017. Of these, 54% (n=83) were

excluded as they resided outside of the study catchment area, 15% (n=23) had a history of seizures prior to 2017, and <1% (n=6) were discussed due to spinal cord lesions and were therefore not relevant to the study. Of the remaining 43 who were eligible for inclusion, 8 had their first seizure during 2017 (19%). Seven of these patients were captured through our previously described methods of ascertainment. One remaining patient diagnosed with epilepsy during the study period was not captured by our methods. This patient was admitted directly under the medical oncology team and the initial clinical query was not of seizure. However, the attending neuro-oncologist felt the recurrent stereotyped events for which the patient was admitted were focal seizures and commenced an A.E.D. The patient did not have an E.E.G. or dedicated brain imaging.

3.5 Discussion

We sought to estimate incidence of first seizures, new diagnosis of epilepsy, and seizure mimics in a defined geographic area adhering to I.L.A.E. guidelines. The I.L.A.E. made a significant change in 2014[6] by introducing the operational definition of epilepsy, allowing a person to be diagnosed with epilepsy following a first unprovoked seizure if there is an estimated 60% or greater risk of recurrent seizures over the next 10 years. The motivation for this change was to allow earlier diagnosis of epilepsy for prevention of unnecessary risk of physical injuries or social consequences of recurrent seizures in patients judged to be susceptible to a high risk of recurrence. In our whole population study, we found that application of the 2014 definition[6] resulted in a 54% higher age-standardised incidence of new diagnosis of epilepsy compared to the 1993 definition.[5] The higher incidence of epilepsy was more pronounced at older ages. There are a number of possible explanations for the observed difference in incidence. First, the 2014 definiton[6] may ‘shift’ the diagnosis to an earlier time-point, creating an early peak in a population whose incidence, if followed for a longer period, would ultimately be the same if the 1993 definition[5] were applied. According to the 2014 definition,[6] a follow up period of 10 years is needed to

verify if such a shift has occurred. Alternatively, or concurrently, the 2014 definition[6] may be less specific than the 1993 definition,[5] allowing diagnosis of epilepsy in persons who will never go on to have a second seizure. This issue is complicated by commencement of an A.E.D. that, at least in the short-term, reduces the risk of a second seizure.

The annual incidences we report when using the 1993 definition[5] and the 2014 definition[6] appear to diverge as age increases. In those up to 10 years of age, the incidence was 28% higher whereas in those over 45 years of age the incidence was 78% higher using the 2014 definition.[6] Structural aetiologies such as brain tumours and cerebrovascular disease are more prevalent in older populations, and may therefore lead to a higher incidence when the 2014 definiton[6] is applied.

Aaberg et al.,[7] reported a 3% higher annual incidence of epilepsy in a cohort of Norwegian children aged 0 to 10 years when the 2014 definition[6] was applied compared to the 1993 definition.[5] The annual incidence of epilepsy in children aged 0 to 10 years according to the 2014[6] definition was similar in our population compared to the Norwegian cohort, specifically 68 versus 72 per 100,000. However, the annual incidence according to the 1993[5] definition was lower in our population, 53 compared to 70 per 100,000 in the Norwegian cohort, resulting in a greater proportionate change. One possible explanation could be that a smaller proportion of children in our population had two seizures during the study period. We undertook our study in 2017 when the 2014 operational definiton[6] was in place whereas the I.L.A.E. definition changed during the Norwegian study period. It is possible that children were commenced on an A.E.D. at an earlier stage in our population resulting in lower second seizure rates, though further investigation of this point is necessary to clarify this. Aaberg et al.,[7] suggested that application of the new definition may be most relevant in adult populations, as has been shown by our data.

In practical terms, the diagnosis of epilepsy often translates to a patient being commenced on an A.E.D. Our data demonstrated that over 90% of patients were

prescribed an A.E.D. in both the 1993[5] and 2014[6] definition groups. From a healthcare management and planning point view, these patients require longitudinal care.

In daily clinical practice, determining if a patient has an approximate 60% or greater risk of recurrent seizures can be difficult, particularly if seizures occur with no apparent cause. Some studies aid clinicians in specific circumstances, for example if a patient has a remote history of a cortical infarct.[18] The Multicentre Trial for Early Epilepsy and Single Seizures (M.E.S.S.)[24] attempted to clarify risk for patients who had a single unprovoked seizure and in whom neither the doctor or patient had a strong view as to whether to start an A.E.D. However, that study did not include neuroimaging as part of risk assessment. There remains a lack of up-to-date, prospective studies to aid clinicians in accurately assessing risk for an individual patient, especially if a person has more than one risk factor for development of epilepsy. Neurologists and physicians may act on experience and gestalt rather than evidence when prescribing an A.E.D. when a patient presents after a first seizure. Importantly, the 2014 definition[6] does not require the clinician to estimate the risk exactly. While this is important clinically, given the absence of specific data in many cohorts, this issue may make future comparisons between epidemiologic studies difficult as an operational definition which allows clinician's experience to inform risk may not be standardised across countries or even regions. To our knowledge, this study is the first to report whole population incidence data since the 2014 definition[6] update and therefore provides useful and current information to practicing physicians, neurologists, epileptologists and epidemiologists.

The diagnostic issue of seizure-mimics is one that is frequently encountered by clinicians. Though it is known that epilepsy and seizures are subject to misdiagnosis,[25] to our knowledge, no incidence data of seizure mimics within a defined population have been reported. Our study is unique in that seizure mimics were captured simultaneously with first seizures and epilepsy cases, and therefore provides an opportunity to compare the occurrence of these disorders within a population over a given period of time using the same methodology. We

were careful to include only patients where the working diagnosis was explicitly stated as a 'seizure' by frontline medical personnel.
By combining the standardised incidence of first seizures and seizure mimics demonstrated by our study, healthcare systems can expect 234 presentations per 100,000 per year. However, the burden of seizure mimics may vary significantly between different populations depending on experience of clinical personnel and access to health resources and specialist assessments such as syncope clinics and clinical care pathways. Therefore caution is needed applying this figure to other populations and healthcare systems. Nonetheless in most countries patient presenting with seizure mimics are likely to first present to emergency department staff, general physicians or general neurologists. Only 13% (n=68) of the seizure mimics captured in our population were seen in the rapid access seizure clinic (R.A.S.C.) of whom 13% (n=9) had been commenced on an A.E.D. prior to referral, the majority for convulsive presentations. Similar to first seizures, these cases require significant resources in terms of early investigations. Correct diagnosis of seizure mimics early in the clinical course prevents inappropriate A.E.D. medication and, in some cases, may detect potentially dangerous conditions such as cardiogenic syncope.

The I.L.A.E. has called for further incidence studies with an emphasis on valid, reproducible methodology and detailed reporting of results.[4] A major strength of our study is the use of multiple methods of case ascertainment followed by individual case analysis in a previously unstudied geographic area and reporting of results in accordance with updated I.L.A.E. definitions[6] and classification systems.[12] In terms of epidemiologic data, our methodology highlights some important issues. First, based on our results, studies which rely heavily on human participants to alert investigators of potential cases may significantly under-ascertain cases, as evidenced by the fact that the majority of our cases came from hospital-based databases. Furthermore, with regard to our assessment of under ascertainment, the single case which was not identified relied solely on reporting by healthcare personnel for inclusion as the person did not have specific radiology or neurophysiology tests for a potential seizure. This highlights the understandable difficulty in recall for busy clinicians and nurse

specialists, and the importance of health record data to aid epidemiologic studies. Second, while E.E.G. databases provided the largest number of cases, only 56% of cases were identified by this method, underlining the need for multiple methods of case ascertainment. In our study, all but three cases were identified by five or fewer methods of ascertainment, despite up to 8 being possible. Within the practical confines of our healthcare setting, this demonstrates maximal use of the available case ascertainment methods.

Over the last four decades, ascertainment methods for epidemiologic studies have progressed and guidelines for accurate methodologies and reporting of epidemiologic studies[4, 9] allow easier comparison between studies. Table 3.3 compares the current study to previously published whole population data in terms of case ascertainment methodology and incidence results. When using the 1993 I.L.A.E. definition[5] of epilepsy, our results are within the range of other studies in industrialised countries. Furthermore, the bimodal age-specific incidence shown in our study has been previously documented in other populations,[26, 27, 29-31, 35, 37, 39, 43] reinforcing the validity of our results. As previously noted, incidence of epilepsy appears to be highest in developing countries,[28, 32, 38, 39] possibly due to the presence of central nervous system infections, consanguinity and perinatal risk factors.[3] Application of the 2014 definition[6] to these populations could result in even higher incidence of epilepsy.

The vast majority of cases of first seizures are referred to secondary or tertiary level care in the geographic area studied. The R.A.S.C. operates a 3-4 week waiting list for new referrals and is readily accessible to G.P.s. The majority of G.P.s would not commence or titrate A.E.D.s in the community without specialist input. An exception may be a patient with advanced dementia or physical disability who may be treated locally by the G.P., thus prompting community survey as part of our case ascertainment. Four percent (n=51) of cases were ascertained by either G.P. or nursing home survey, of which 10% (n=5, <1% of total) were unique to community based ascertainment methods (data not shown). The low level of ascertainment is likely explained by the our sampling frequency; we wrote to G.P.s on a three monthly basis and nursing homes on a

six monthly basis[10] and therefore recall of new cases can be understandably low. MacDonald et al.,[33] were unique in their intense liaison with a cohort of 13 practises in whom all G.P.s agreed to actively participate in order to identify all incident neurological diagnosis. It would not have been practical within the geographic area included in our study, which included over 350 G.P.s and 120 nursing home and residential care facilities, to liaise on a more regular basis. For the reasons outlined above, we do not expect that the low level of ascertainment from community sources will have resulted in significant under-ascertainment of unique cases.

Unlike many previous studies, we did not use hospital medical record coding data. Hospital Inpatient Enquiry (H.I.P.E.) data in Ireland is not designed for research and the validity of H.I.P.E. data with regard to epilepsy is unknown. Furthermore, seizures occurring in medically unwell patients admitted for other reasons may not be coded. H.I.P.E. data does not differentiate between new onset seizures and admission for established epilepsy. Finally, H.I.P.E. data is not available for private hospitals. Hernandez-Ronquillo et al.,[26] and Giussani et al.,[27] using solely medical record coding data, report higher crude annual incidence than in our population. However, individual case validation was not performed in either study and therefore accuracy of diagnosis and coding is unknown. In contrast, Annegers et al.,[34] used coded data to identify cases followed by individual case validation and report annual incidence lower than our population, which may be explained by the small numbers of persons over 65 years in that study. In populations with a very well developed and detailed medical record linkage database, such as Rochester Minnesota,[37, 43] information on seizure and epilepsy type can be obtained. However, H.I.P.E. data in Ireland does not provide this level of detail. Therefore, we did not anticipate that hospital medical record data would significantly improve either the sensitivity of case ascertainment or the detail of case classification in our population.[10] Ultimately, the case ascertainment methods used in a particular population must be individually designed for maximal case ascertainment within the confines of the healthcare system of that population.[4]

We acknowledge that some patients may have a first seizure in 2017 and not seek medical attention. For some of these patients a diagnosis of epilepsy will be made in the future if they present with further seizures. On the other hand, there is no reason to expect that the number of these potentially missed cases would differ from the numbers of patients included who had seizures prior to 2017 but first sought medical attention in 2017, yielding no net loss in incidence.

In summary, using multiple methods of case ascertainment we estimated the incidence of first seizures (provoked and unprovoked), new diagnosis of epilepsy and seizure mimics. Application of the 2014 I.L.A.E. definition of epilepsy[6] resulted in just over 50% increase in the incidence of new diagnosis of epilepsy compared to the 1993 definition.[5] We found that seizures, epilepsy and seizure mimics each represent a significant burden to health care systems.

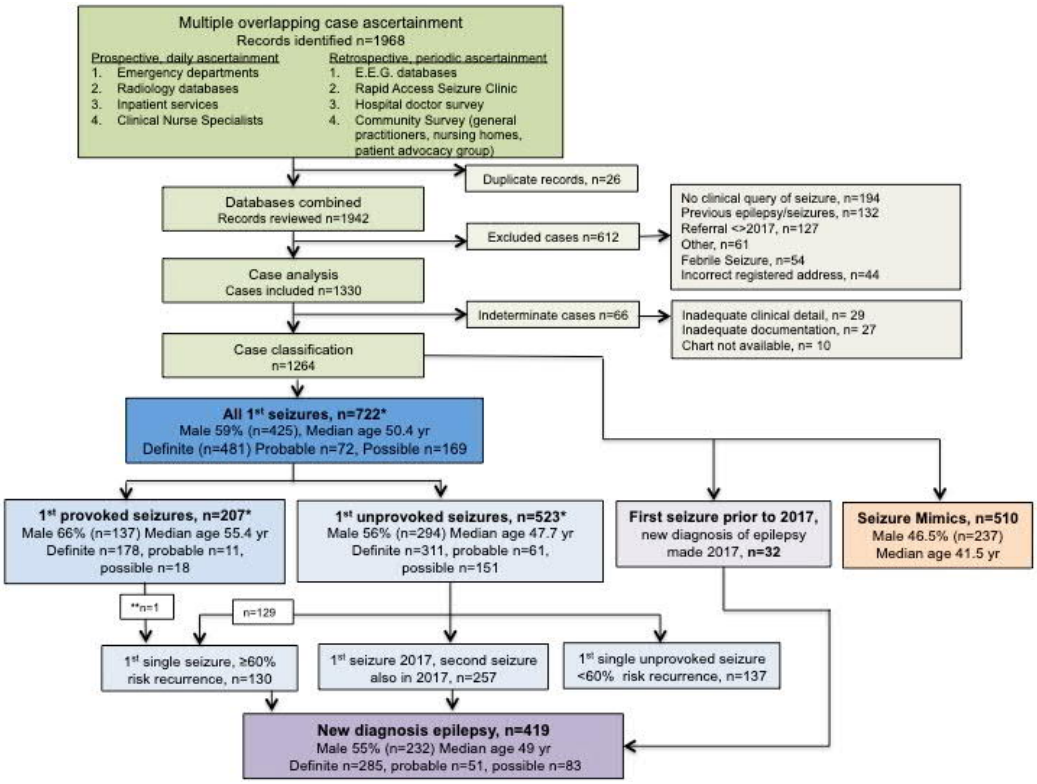
3.6 Acknowledgements

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3.7 Figures

Figure 3.1 Study overview.

Multiple overlapping retrospective and prospective case ascertainment methods were applied to the defined area from 1st January 2017 to 31st March 2018 to identify all potential cases of first seizure and new diagnosis of epilepsy that occurred during the calendar year 2017. Included cases (n=1264) were categorised as definite, probable or possible first single seizure (provoked or unprovoked) or new diagnosis of epilepsy based on I.L.A.E. epidemiologic guidelines.[4] Cases in whom an alternate diagnosis was reached were classified as seizure mimics.[14]



[14] *Eight cases had both a first provoked and first unprovoked seizure during the study period. ** One case of a first provoked seizure was deemed to also be at significantly increase risk of recurrent seizures and was therefore also classified as epilepsy. EEG= electroencephalogram, yr= years.

Figure 3.2 Unadjusted annual incidence.

Unadjusted age group specific annual incidence for definite and probable first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics per 100,000 population during the calendar year 2017.

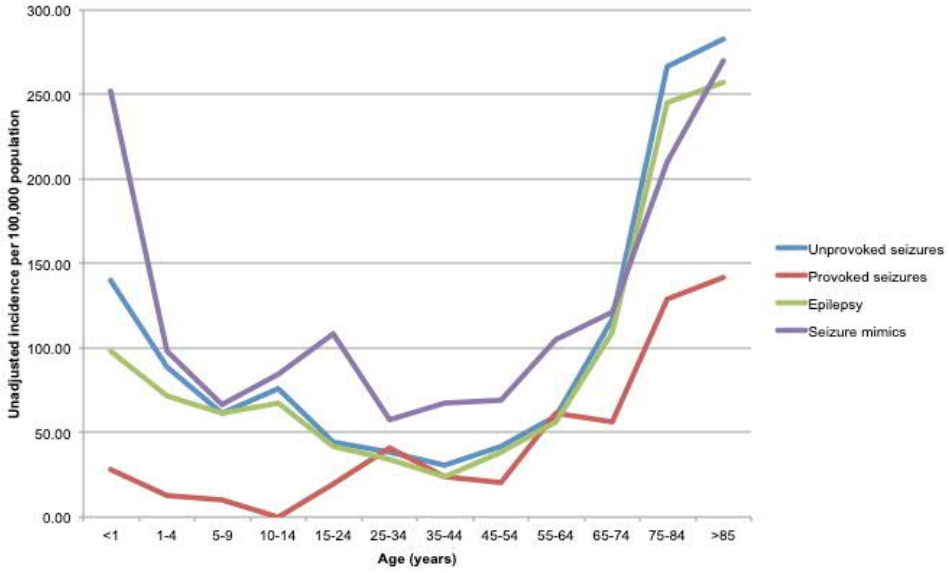


Figure 3.3 The annual incidence of epilepsy according to the 1993[5] and 2014[6] I.L.A.E. definitions.

The unadjusted annual incidence of definite and probable new diagnosis of epilepsy according to the 1993 and 2014 I.L.A.E. definitions of epilepsy in the study population during the calendar year 2017.

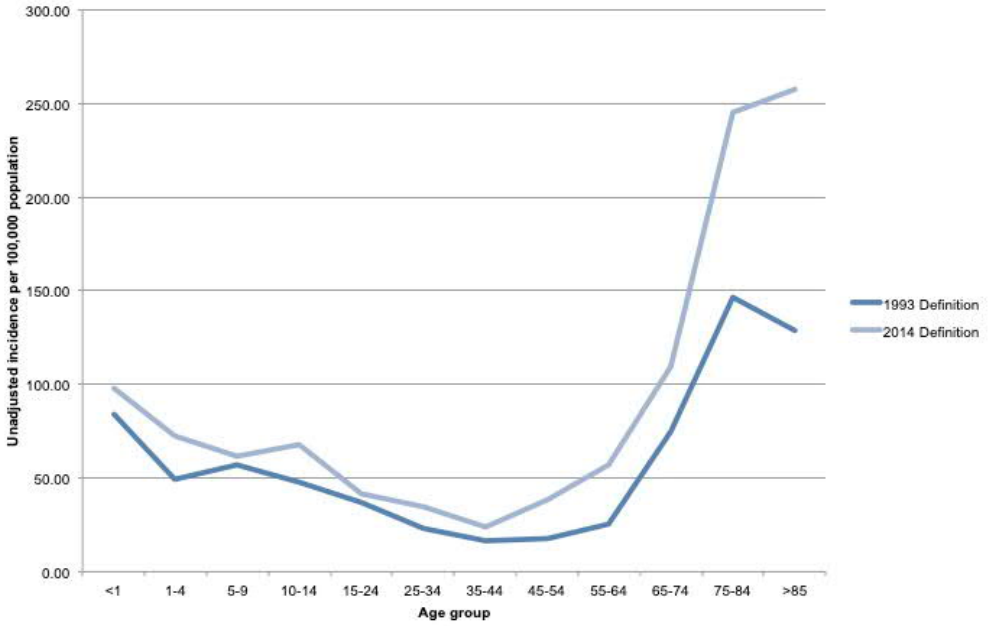
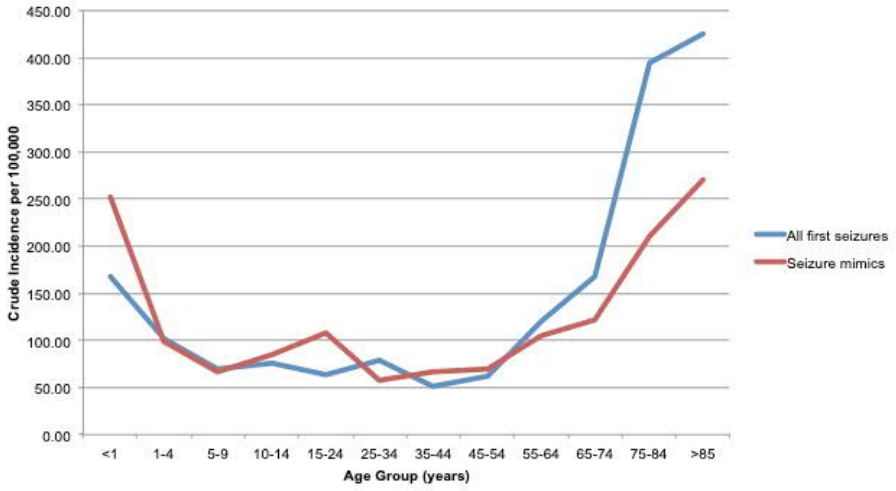


Figure 3.4 The annual incidence of all first seizures compared to all seizure mimics

Unadjusted age group specific annual incidence of all definite and probable first seizures and seizure mimics during the calendar year 2017.



3.8 Tables

Table 3.1 The sex-specific, age-group specific and total unadjusted and age- standardised incidence of all definite and probable first seizures, definite and probable first unprovoked seizures, definite and probable first provoked seizures, definite and probable new diagnosis of epilepsy and seizure mimics in the defined geographic area for the calendar year 2017.[15]

Annual incidence of all first seizures

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total population	Cases	Incidence
<1	3677	7	190	3466	5	144	7143	12	168
1-4	15491	23	148	15008	8	53	30499	31	102
5-9	20625	18	87	19820	10	50	40445	28	69
10-14	18191	19	104	17253	8	46	35444	27	76
15-24	33952	28	82	33394	15	45	67346	43	64
25-34	35248	41	116	37596	16	43	72844	57	78
35-44	41970	26	62	42861	17	40	84831	43	51
45-54	36309	28	77	36000	17	47	72309	45	62
55-64	29092	41	141	29072	29	100	58164	70	120
65-74	21084	40	190	21732	32	147	42816	72	168
75-84	10440	52	498	12822	40	312	23262	92	395
>85	2596	9	347	5169	24	464	7765	33	425
Total	**268675**	**332**	**124**	**274193**	**221**	**81**	**542868**	**553**	**102**
95%CI			(111-138)			(71-92)			94-111
	Male:female incidence ratio				1.53	Age standardised incidence			123

Annual incidence of first unprovoked seizures

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total population	Cases	Incidence
<1	3677	6	163	3466	4	115	7143	10	140
1-4	15491	20	129	15008	7	47	30499	27	89
5-9	20625	16	78	19820	9	45	40445	25	62
10-14	18191	19	104	17253	8	46	35444	27	76
15-24	33952	19	56	33394	11	33	67346	30	45
25-34	35248	19	54	37596	9	24	72844	28	38
35-44	41970	14	33	42861	12	28	84831	26	31
45-54	36309	17	47	36000	13	36	72309	30	41
55-64	29092	21	72	29072	14	48	58164	35	60
65-74	21084	27	128	21732	23	106	42816	50	117
75-84	10440	29	278	12822	33	257	23262	62	267
>85	2596	7	270	5169	15	290	7765	22	283
Total	**268675**	**214**	**80**	**274193**	**158**	**58**	**542868**	**372**	**69**
95%CI			70-91			49-67			62-76
	Male:female incidence ratio				1.38	Age standardised incidence			83

Annual incidence of first provoked seizures

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total population	Cases	Incidence
<1	3677	1	27	3466	1	29	7143	2	28
1-4	15491	3	19	15008	1	7	30499	4	13
5-9	20625	3	15	19820	1	5	40445	4	10
10-14	18191	0	0	17253	0	0	35444	0	0
15-24	33952	9	27	33394	4	12	67346	13	19
25-34	35248	23	65	37596	7	19	72844	30	41
35-44	41970	15	36	42861	5	12	84831	20	24
45-54	36309	11	30	36000	4	11	72309	15	21
55-64	29092	21	72	29072	15	52	58164	36	62
65-74	21084	13	62	21732	11	51	42816	24	56
75-84	10440	23	220	12822	7	55	23262	30	129
>85	2596	2	77	5169	9	174	7765	11	142
Total	**268675**	**124**	**46**	**274193**	**65**	**24**	**542868**	**189**	**35**
95%CI		39-55				19-30			30-40
	Male:female incidence ratio				1.95	Age standardised incidence			42

[15] M:F IR= male to female incidence ratio, 95%CI =95% Confidence interval

Table 3.1 contd. The sex-specific, age-group specific and total unadjusted and age- standardised incidence of all definite and probable first seizures, definite and probable first unprovoked seizures, definite and probable first provoked seizures, definite and probable new diagnosis of epilepsy and seizure mimics in the defined geographic area for the calendar year 2017. [16]

Annual incidence of new diagnosis of epilepsy according to the 2014 I.L.A.E. definition									
Age groups	**Males**	**Cases**	**Incidence**	**Females**	**Cases**	**Incidence**	**Total population**	**Cases**	**Incidence**
<1	3677	5	136	3466	2	58	7143	7	98
1-4	15491	16	103	15008	6	40	30499	22	72
5-9	20625	16	78	19820	9	45	40445	25	62
10-14	18191	16	88	17253	8	46	35444	24	68
15-24	33952	16	47	33394	12	36	67346	28	42
25-34	35248	16	45	37596	9	24	72844	25	34
35-44	41970	13	31	42861	7	16	84831	20	24
45-54	36309	16	44	36000	12	33	72309	28	39
55-64	29092	20	69	29072	13	45	58164	33	57
65-74	21084	25	119	21732	22	101	42816	47	110
75-84	10440	26	249	12822	31	242	23262	57	245
>85	2596	6	231	5169	14	271	7765	20	258
Total	**268675**	**191**	**71**	**274193**	**145**	**53**	**542868**	**336**	**62**
95%CI			62-82			45-62			56-69
	Male:female incidence ratio				1.34	Age standardised incidence			74
Annual incidence of seizure mimics									
Age groups	**Males**	**Cases**	**Incidence**	**Females**	**Cases**	**Incidence**	**Total population**	**Cases**	**Incidence**
<1	3677	10	272	3466	8	231	7143	18	252
1-4	15491	19	123	15008	11	73	30499	30	98
5-9	20625	16	78	19820	11	55	40445	27	67
10-14	18191	17	93	17253	13	75	35444	30	85
15-24	33952	24	71	33394	49	147	67346	73	108
25-34	35248	18	51	37596	24	64	72844	42	58
35-44	41970	20	48	42861	37	86	84831	57	67
45-54	36309	28	77	36000	22	61	72309	50	69
55-64	29092	27	93	29072	34	117	58164	61	105
65-74	21084	25	119	21732	27	124	42816	52	121
75-84	10440	21	201	12822	28	218	23262	49	211
>85	2596	12	462	5169	9	174	7765	21	270
Total	**268675**	**237**	**88**	**274193**	**273**	**100**	**542868**	**510**	**94**
95%CI			78-100			88-112			86-102
	Male:female incidence ratio				0.89	Age standardised incidence			111

[16] M:F IR= male to female incidence ratio, 95%CI =95% Confidence interval

Table 3.2 The sex-specific, age-group specific and total crude and age- standardised incidence of definite and probable new diagnosis made according to the 1993 I.L.A.E. definition of epilepsy.[5][17]

Annual incidence of epilepsy according to the 1993 I.L.A.E. definition of epilepsy									
Age groups	**Males**	**Cases**	**Incidence**	**Females**	**Cases**	**Incidence**	**Total population**	**Cases**	**Incidence**
<1	3677	4	109	3466	2	58	7143	6	84
1-4	15491	10	65	15008	5	33	30499	15	49
5-9	20625	15	73	19820	8	40	40445	23	57
10-14	18191	10	55	17253	7	41	35444	17	48
15-24	33952	14	41	33394	11	33	67346	25	37
25-34	35248	10	28	37596	7	19	72844	17	23
35-44	41970	10	24	42861	4	9	84831	14	17
45-54	36309	7	19	36000	6	17	72309	13	18
55-64	29092	9	31	29072	6	21	58164	15	26
65-74	21084	16	76	21732	16	74	42816	32	75
75-84	10440	14	134	12822	20	156	23262	34	146
>85	2596	4	154	5169	6	116	7765	10	129
Total	268675	123	46	274193	98	36	542868	221	41
95%CI			38-55			29-44			36-46
	Male:female incidence ratio				1.28	Age standardised incidence			48

[17] M:F Ratio= male to female incidence ratio.

Table 3.3 Comparison of case ascertainment methods, crude and age-adjusted incidence values from previous studies investigating the incidence of epilepsy and/or first seizures in all ages within a defined population.

Studies included were whole population studies including both adults and children over 28 days old.[18]

Study	Current study	Hernández-Ronquillo et al., 2018[26]	Giussani et al., 201[27]	Winkler et al., 2009[28]	Benn et al., 2008[29]	Christensen et al., 2007[30]	Olafsson et al., 2005[31]	Medina et al., 2005[32]	MacDonald et al., 2000[33]	Annegers et al., 1999[34]	Mani et al., 1998[35]	Tekle-Haimanot et al., 1997[36]	Hauser et al., 1993[37]	Lavados et al., 1992[38]	Rwiza et al., 1992[39]	Joensen 1986[40]	Li et al., 1985[41]	Granieri et al., 1983[42]	Hauser and Kurland, 1975[43]	De Graaf 1974[44]
Geographic area (population)	Cork, Ireland, (542,868)	Saskatchewan Canada (1,033,381)	Lecco, Italy (311,637)	Northern Tanzania (41,937)	New York, U.S. 270,677)	Denmark (6,543,341)	Iceland, (882,151)	Salamá, Honduras (6,473)	London, United Kingdom, (100,230)	Houston, Texas, U.S. (c.600,000)	Southern India (64,963)	Rural Ethiopia (61,686)	Rochester, United States (c. 40,000)	Northern Chile (17,694)	Ulanga Tanzania (138,837)	Faroe Island (41,144)	China (63, 195)	Copparo, Italy (45,153)	Rochester, United States (c.34,678)	Norway (215,000)
Case ascertainment																				
Radiology database	X						X													
EEG database	X						X									X		X		X
Emergency Department	X				X		X													
Neurologists/Paediatricians	X				X		X											X		
Other hospital specialists	X						X													
RASC	X								X											
Clinical Nurse Specialist	X																			
GP survey	X						X		X							X		X		
Residential care survey	X				X		X													
Patient Advocacy Group	X																			
Hospital medical record data		X	X		X	X			X	X			X	X				X	X	X
Door to door survey				X				X			X	X			X		X			
School teachers and social workers																		X		
Crude incidence of epilepsy (per 100,000) 1993 I.L.A.E. definition	41	63	53.41	81		68.8	33.3	92.7		35.5	49.3	64		113	73.3	42.8		33.1	48.7	32.8
Age-adjusted incidence of epilepsy (per 100,000) 1993 I.L.A.E. definition	48 adjusted to Europe	62 adjusted to Canada	44.74 adjusted to world		16.4 adjusted to U.S.		32.4 adjusted to Europe		46 adjusted to U.K.			49 adjusted to U.S.	44 adjusted to U.S.	108 adjusted to Chile			35 adjusted	38.3 adjusted to Italy		
Incidence of epilepsy (per 100,000) 2014 I.L.A.E. definition	74 age adjusted to Europe																			

[18] AED =Anti-epileptic drug. EEG= electroencephalogram. RASC= Rapid Access Seizure Clinic. GP= General practitoner.

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Chapter 4 Association between social deprivation and the incidence of first seizures, new diagnosis of epilepsy and seizure mimics

In this chapter of my PhD thesis, I divided the population of Cork city and county into five distinct quintiles based on a relative measure of socioeconomic deprivation, accessed through the Central Statistics Office following the 2016 Census of population. I analysed the incidence of first seizures, new diagnosis of epilepsy and seizure mimics in each of the quintiles to determine if relatively low socioeconomic deprivation was associated with an increased incidence of each of the four diagnostic categories. Co-authors are Dr. Paul Corcoran, Dr. Daniel Costello and Dr.Éilis O'Reilly.

This chapter of my PhD thesis will be submitted to *Neurology* journal as an original research article.

4.1 Abstract

Objective: Previous epidemiologic studies have investigated whether social deprivation is associated with higher incidence of epilepsy. However results are conflicting, especially in children. Furthermore, the mechanisms underlying a potential association are unclear. This study examines whether there is an association between social deprivation and the incidence of first seizures (unprovoked and provoked), newly-diagnosed epilepsy and seizure mimics in a validated patient cohort.

Methods: Multiple methods of case identification followed by individual case validation and classification were carried out in a defined geographic area (population 542,868) to identify all incident cases of first seizure (provoked and unprovoked), new diagnosis of epilepsy and seizures mimics presenting during the calendar year 2017. Seizure mimics were defined as patients in whom a working diagnosis of seizure was considered, but where an alternate diagnosis was subsequently reached. An area-level relative deprivation index based on 10 indicators from census data was assigned to each patient according to postal address on record. The annual incidence per 100,000 population was calculated and compared for each of five quintiles of increasing social deprivation.

Results : The annual incidence of first unprovoked seizures (n=372), first provoked seizures (n=189), new diagnosis of epilepsy (n=336) and seizure mimics (n=510) was highest in the most deprived areas compared to the least deprived areas (incidence ratio of 1.79 (95%CI 1.26, 2.52), 1.55 (95%CI 1.04, 2.32), 1.83 (95%CI 1.28, 2.62) and 1.30 (95%CI 1.00, 1.69), respectively). This finding was robust in both adults and children and in those with structural, genetic and unknown aetiologies of epilepsy.

Conclusions: The incidence of seizures, epilepsy and seizure mimics is associated with increased social deprivation. The reasons for this higher incidence is likely to be multifactorial. Areas of social deprivation require increased services to address diagnostic and treatment requirements.

4.2 Introduction

Epilepsy is a chronic neurological disorder characterised by recurrent, unprovoked seizures and by the neurobiologic, cognitive, psychological and social consequences of the condition.[1] Potential social consequences of the disease include loss of earnings, loss of driving privileges, social isolation and stigma. These consequences put an individual at risk of downward social drift following a diagnosis of epilepsy. Studies have shown an association between social deprivation and prevalence of epilepsy.[2-4] Higher prevalence of epilepsy among residents living in socially deprived areas may be due to social drift, or to social causation, whereby factors associated with social deprivation put an individual at risk of epilepsy,[5] or to a combination of both these factors. Incidence studies that calculate a level of social deprivation for persons at the timepoint when they had their first seizure are necessary to establish if social deprivation is associated with the development of seizures and epilepsy and to identify and ameliorate potential risk factors. Furthermore, if certain social strata have a higher incidence of epilepsy, health care provision and resources should reflect their increased needs.

In 1990, a case-referent study from Northern Sweden investigating the incidence of unprovoked epileptic seizures in adults found no difference in sociodemographic factors between cases and controls.[6] More recently, a 2002 study in an unselected population served by 20 unselected general practices in the United Kingdom (U.K.)[7] followed for 18-24 months demonstrated that the incidence of epilepsy in the most deprived fifth of the population was 2.33 times higher than the least deprived fifth using an index of social deprivation based on four variables available from census data. Further adjustment for whether the practice was in London attenuated the findings. However, this may represent over-adjustment given that populations served by the eight London practices were in more deprived areas. A strong correlation between epilepsy incidence and social deprivation, using a census based index of social deprivation, was

reported from a Welsh medical record linkage study,[5] with annual incidence in the most deprived decile twice that of the least deprived decile. The aetiology and classification of epilepsy was not reported in either of these studies. Finally, a community-based study in New York carried out between 2003 and 2005 reported a higher incidence of unprovoked seizures in low income compared to high-income households.[8]

Results from studies investigating the incidence of epilepsy in children in socially deprived areas have been conflicting. Using an area level measure of deprivation, no difference was found in the incidence of epilepsy across four quartiles of social deprivation in 155 children aged 29 days to 14 years old in the U.K.[9] In contrast, living in a high-deprivation neighbourhood in Sweden increased the odds of hospital registration for childhood and adolescent epilepsy by 1.15 compared to those living in low-deprivation neighbourhoods.[10] Finally, a case-control study from Iceland[11] found that low socioeconomic status, as measured by low individual-level educational attainment or lack of home ownership, increased the risk of incident epilepsy in adults, whereas no markers of socioeconomic status were associated with incident epilepsy in children. To our knowledge no study to date has reported if the incidence of provoked seizures or of diagnosis with a seizure mimic differs between areas of relatively low and high social deprivation.

Using multiple overlapping methods of case ascertainment, assessment of under-ascertainment and individual case validation,[12] we previously published the incidence of first seizures, epilepsy and seizure mimics in adults and children in a defined geographic region of Ireland.[13] We further sought to determine if the incidence of first seizures, new diagnosis of epilepsy and seizure mimics in our whole population cohort differed between areas of relatively high social deprivation compared to areas of relatively low social deprivation and to clarify if any association is specific to children or adults. Furthermore, we sought to investigate if certain aetiologic categories of epilepsy are associated with social deprivation. Finally, we sought to determine if the incidence of provoked

seizures and seizure mimics differed between areas of relatively high social deprivation compared to areas of relatively low social deprivation.

4.3 Methods

This study was carried out in the geographically defined area of Cork city and county, Ireland, with an estimated population of 542,868 adults and children based on national census data from 2016. The area contains one large urban development which encompasses approximately one quarter of the total population (125,657 adults and children). The remaining population lives in smaller towns, villages or rural dwellings. The geographic area spans approximately 7,500 km^2. The Irish healthcare system consists of both public and private hospitals. Patients may either self-present to the emergency department, or are referred to the emergency department or outpatients department by their general practitioner (G.P.).

4.3.1 Case ascertainment and classification

A detailed description of the epidemiologic protocol applied to this population has been previously published.[12] In brief, multiple over-lapping sources of case ascertainment were applied to the geographically defined area from 1st January 2017 to 31st March 2018 in order to capture all cases of possible first seizures, new diagnosis of epilepsy and seizure mimics whose first interaction with medical service for the event occurred during the calendar year 2017. Case ascertainment utilized a combination of prospective and retrospective methods in both community and hospital settings. All patients who presented to medical services during the calendar year 2017 with a possible first seizure or new diagnosis of epilepsy whose address, as per the hospital based administrative system, was within the geographically defined area were included. In accordance with the I.L.A.E. epidemiologic guidelines,[14] neonatal seizures and febrile seizures were excluded. Cases with inadequate or unclear documentation were classified as indeterminate and were not included in analysis. Epileptic seizures

and epilepsy were defined according to the I.L.A.E. operational definitions.[1, 15] Provoked seizures[16] were identified as a specific sub-cohort, and were separated from first unprovoked seizures and epilepsy during analysis.

Following identification of a potential case, the medical chart and investigations of the patient were reviewed first-hand. In accordance with the I.L.A.E. epidemiologic study guidelines,[14] the probability that an event was a seizure or not, was defined as either a definite, probable or possible seizure, based on the evidence available, see our previously published methodology[17] for more detailed discussion. Cases who initially had a working diagnosis of seizure as judged by a first-line decision-maker (for example, an emergency department physician, G.P. or advanced paramedic), but who were ultimately determined not to have had a seizure (by an epileptologist, senior neurologist or senior physician), were classified as 'seizure mimics'. For all definite and probable cases of epilepsy the aetiology was classified according to the 2017 I.L.A.E. classification[18] as structural, genetic, immune, infectious, metabolic or unknown. Patients with underlying developmental abnormalities, such as autism or intellectual disability, of unspecified or unknown cause were classified as unknown. During review of the medical record, where documented, risk factors for seizures and epilepsy were collected. These included a history of febrile seizures, history of central nervous system infection, history of developmental delay, family history of epilepsy, history of drug or alcohol abuse, history of head injury, history of cerebrovascular disease or history of psychiatric illness.

4.3.2 Measure of socioeconomic status

Electoral divisions (El.D.s) are the smallest legally defined administrative areas in Ireland. Information gathered via the population census is available publically and includes the age group and gender of persons living in each El.D. There are 398 El.D.s within Cork city and county. Each case included in the study was assigned an El.D. based on their registered address according to the hospital administrative data. Cases whose registered address was in a nursing home or

residential care setting (n=18), convent (n=5), prison (n=2) or homeless (n=5) were not assigned El.D. and were not included in the socioeconomic analysis.

The 2016 Pobal HP Deprivation Index[19] draws on data from the 2016 Census of Population. A Relative Deprivation Index (R.D.I.) is calculated for each census wave by a factor analytical approach which combines 10 indicators: percentage change in population over the previous 5 years, percentage change in population under 15 or over 64 years of age, percentage of population with primary school education only, percentage of population with third level education, percentage of single parent households, mean number of persons per room, percentage of households headed by professionals, percentage of households headed by semi-skilled or unskilled manual workers, male and female unemployment rates. Each El.D. within the country is assigned a R.D.I. based on the census data collected within that El.D. For each census year, the R.D.I. in Ireland has a mean Deprivation Index of zero and a standard deviation of 10.

In order to assess if the incidence of first seizures, newly diagnosed epilepsy and seizure mimics differs between areas of relatively high deprivation compared to areas with relatively low deprivation, each El.D. within the defined geographic area was ranked according to its R.D.I. from most deprived to least deprived. The El.D.s were then divided into five quintiles with approximately one fifth of the population i.e., approximately 180,000 persons, in each quintile. Quintile 1 refers to the relatively most deprived one fifth of the population of the defined geographic area. Quintile 5 refers to the relatively least deprived one fifth of the population. The sex-specific population of each group was calculated using publicly available information from the Central Statistics Office (C.S.O.). C.S.O. provides data on the number of people within certain age brackets, therefore it was not possible to calculate the median age of the base population quintiles.

4.3.3 Statistical analysis

The annual incidence of first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics in each quintile was calculated by dividing the number of people with a new diagnosis during the calendar year 2017 by the number of people at risk in that quintile and expressing it per 100,000 population. While we assume that the whole population is at risk because the prevalence within each deprivation quintile is unknown, the relatively high number at risk for each outcome, for example 990 per 1,000 for new diagnosis of epilepsy[20] means that the incidence and incidence ratios are only slightly deattenuated. Ninety-five percent confidence intervals (95%CI) were calculated using the Mid-P exact test. Incidence ratios and 95%CI were used to compare incidence in the least deprived quintile to the most deprived quintile. Incidence ratios were deemed to be statistically significant for $p<0.05$. Statistics were performed using SPSS version 26 for Mac.

In order to determine if the incidence ratio in each diagnostic category comparing the least and most deprived quintiles was modified by age, we determined the population of children less than 15 years of age in each quintile using data from the C.S.O. Annual incidence and incidence ratios were calculated for the population between 0 to 14 years of age and for those 15 years of age and older.

We determined the number of cases of new diagnosis of epilepsy with a structural, genetic or unknown aetiology in each of the five population quintiles and calculated the annual incidence of each diagnosis based on the publicly available age and gender specific data as outlined above.

Finally, we investigated if there was a difference in the prevalence of specific risk factors (history of febrile seizures, history of central nervous system infection, history of developmental delay, family history of epilepsy, history of drug or alcohol abuse, history of head injury, history of cerebrovascular disease or

history of psychiatric illness) for epilepsy in those with a new diagnosis of definite or probable epilepsy between each of the five quintiles.

4.3.4 Ethics

The study protocol was approved by the local clinical ethics research committee (ECM (dd) 15/11/16, ECM (hh) 06/12/16 and EDM (ff) 07/02/17, Appendix 1). Following ascertainment, data were anonymised prior to analysis and storage.

4.4 Results

During the calander year 2017, in the defined geographic area, 372 people were diagnosed with a definite or probable first unprovoked seizure, 189 people were diagnosed with a definite or probable first provoked seizure, 336 people were diagnosed with a definite or probable new diagnosis of epilepsy and 510 people were diagnosed with a seizure mimic. Briefly, the incidence of first unprovoked seizures was 69 per 100,000 population (age-standardised 83); first provoked seizure was 35 per 100,000 (age-standardised 42). The incidence of new diagnosis of epilepsy was 62 per 100,000 (age-standardised 74). Finally, the incidence of seizure mimics was 94 per 100,000 (age-standardised 111). Age and gender specific incidence have been previously published.[13]

Table 4.1 shows the number of cases and mean R.D.I. of cases within each R.D.I. quintile for each of the four diagnostic categories of first unprovoked seizure, first provoked seizure, new diagnosis of epilepsy, and seizure mimics. For each diagnostic category, the incidence was higher in the most deprived quintile compared to the least deprived quintile, see Table 4.2 and Figure 4.1. In particular, the incidence ratio of the most deprived quintile compared to the least deprived quintile was 1.79 (95%CI 1.26, 2.52) for first unprovoked seizure, 1.55 (95%CI 1.04, 2.32) for first provoked seizure, 1.83 (95%CI 1.28, 2.62) for new diagnosis of epilepsy and 1.30 (95%CI 1.00, 1.69), for seizure mimics.

When age was dichotomised to separate children (aged 0 to 14 years old) from adults (15 years or older at event) the incidence of first unprovoked seizure and new diagnosis of epilepsy remained highest in the most deprived quintile compared to the least deprived, see Table 4.3. In particular, for persons under 15 years old the incidence ratio comparing the most to least deprived quintile was 1.91 (95% CI 0.91, 3.98) for first unprovoked seizure and 2.20 (95% CI 1.04, 4.68) for new diagnosis of epilepsy. For persons 15 years and older, the incidence ratio was 1.76 (95% CI 1.19, 2.60) for first unprovoked seizure and 1.74 (95% CI 1.16, 2.62) for new diagnosis of epilepsy. With regard to seizure mimics, the incidence remained significantly higher in the most deprived quintile compared to the least deprived quintile for those 15 years of age and older [incidence ratio 1.40 (95%CI 1.05, 1.87) but not for children (incidence ratio 0.90 (95%CI 0.48, 1.69]. The total number of cases of first provoked seizures occuring in those less than 15 years of age was 10 across all quintiles therefore we did not proceed with comparison of children and adults in this diagnostic category.

The annual incidence of new diagnosis of epilepsy in those with a structural aetiology, a genetic aetiology and an unknown aetiology of epilepsy was highest in the most deprived quintile compared to the least deprived. In particular, the incidence ratio was 1.73 (95% CI 1.08, 2.78) for structural, 1.98 (95% CI 0.68, 5.81) for genetic, and 2.15 (95% CI 1.08, 4.26) for unknown aetiologies, see Table 4.4.

Of those whose history was known and documented, the proportion of persons with a new diagnosis of epilepsy with a history of febrile seizures was highest in the most deprived quintile of the population compared to the least deprived quintile of the population, see Table 4.5. Specifically, 19% (n= 11) in Quintile 1 compared to 3% (n=1) in Quintile 5, respectively. Of those whose history was known, the proportion of patients with a family history of epilepsy was lowest in the least deprived quintile (13%, n=4) with relatively similar proportions in the other quintiles [24% (n= 14), 23% (n=15), 19% (n=7) and 24%(n=10) in Quintiles 1 to 4, respectively]. Because data were gathered from retrospective

chart review, a significant proportion of cases in all quintiles had an unknown or undocumented history of epilepsy risk factors. However, for these risk factors, missing response did not correlate with deprivation quintiles.

4.5 Discussion

By using a combination of retrospective and prospective case ascertainment followed by individual case validation and classification,[17] we report that persons living in the most deprived quintile of the defined geographic area studied are 1.79 times more likely to be diagnosed with a first unprovoked seizure ($p<0.001$), 1.55 times more likely to be diagnosed with a first provoked seizure ($p<0.05$), 1.83 times more likely to be diagnosed with new onset epilepsy ($p<0.001$) and 1.3 times more likley to be diagnosed with a seizure mimic ($p<0.05$) than those living in the least deprived quintile of the defined geographic area. Furthermore, we report a higher incidence of new diagnosis of epilepsy in both children ($p<0.05$) and adults ($p<0.01$), a higher incidence of first unprovoked seizures in adults ($p<0.01$) and a trend toward significantly increased incidence of first unprovoked seizures in children ($p=0.08$) in areas of relatively high socioeconomic deprivation compared to areas of relatively low socioeconomic deprivation. Finally, we report a higher incidence of both structural ($p<0.05$) and unknown ($p<0.05$) aetiologies of epilepsy in areas of relatively high sociodemographic deprivation. Similarly, the incidence of epilepsy with a genetic aetiology was higher in areas of relative socioeconomic deprivation, though numbers were small in this group and results were not statistically significant.

Similar to our results, higher incidence of unprovoked seizures and epilepsy in areas of relative socioeconomic deprivation have been reported in adults in England,[7] Wales,[5] Iceland[11] and Northern Manhattan.[8] Although the measure used in each study to determine socioeconomic status differed, concordance of results reinforces the conclusions. In our study, among persons with a new diagnosis of epilepsy for whom it was recorded, 27% (n=50) reported a positive family history. Family history was lowest among those in the least deprived

quintile (13%, n=4) which is not inconsistent with the hypothesis of social drift. However, the trend across quintiles was still evident after accounting for family history. Furthermore, social drift among persons with a diagnosis of epilepsy was not found by comparing the socioeconomic status of cases and controls whose parents had epilepsy in Iceland,[11] or by following a cohort of patients with incident epilepsy for ten years in Wales.[5] Taken together, studies to-date suggest that social causation, rather than social drift, is the dominant factor contributing to the higher prevalence of epilepsy[2-4] in areas of social deprivation. Further work may clarify the relative contributions of both.

Establishing the mechanism of the association between seizures, epilepsy and socioeconomic deprivation is important in order to identify potentially modifiable risk factors. One possible explanation is the increased occurrence of risk factors for development of epilepsy, such as traumatic brain injury, in areas of relatively high social deprivation.[21] However, as we found a higher incidence of structural, genetic and unknown aetiologies of epilepsy in areas of social deprivation, our results suggest that the association may be multifactorial. In contrast, subgroup analysis of adult cases in Iceland found that low socioeconomic status as indicated by low education level of main wage earner and lack of home ownership was significant only in the idiopathic/cryptogenic aetiology subgroup and not in those with a remote symptomatic or progressive symptomatic aetiology. Case numbers in the latter two groups were small, though there remained no difference when these two groups were combined.[11] We applied the updated I.L.A.E. classification systems for seizure[22] and epilepsy[18] type to our cohort, which reflect advances in knowledge of epilepsy mechanisms. Application of these classification systems, which take into account imaging and E.E.G. results, may have resulted in more accurate classification and therefore revealed a true gradient across all aetiologies. However, the number of cases in our study with a genetic aetiology was also small and risk ratios in this subgroup were not statistically significant. Larger studies are necessary to confirm the validity of this result.

Similar to studies in Sweden[10], U.K.[7] and Wales[5], we found the annual incidence of epilepsy in children was higher in the most deprived areas compared to the least deprived areas. The influence of a genetic aetiology of epilepsy may be more relevant in younger persons than in adults, in whom focal epilepsy becomes more common. A genetic predisposition may be suggested by a positive family history of epilepsy and by a history of febrile seizures, both of which were more common in the most deprived population quintiles compared to the least deprived quintiles. However, as our data were obtained from retrospective chart review, a proportion of cases in each quintile had an unknown or undocumented risk factor. For most risk factors, the proportion of those without a documented history of a risk factor was similar between quintiles. However, it is difficult to draw firm conclusions with regard to specific risk factors from our study. Future prospective studies specifically investigating risk factors for seizures and epilepsy among incident cases from areas of varying levels of socioeconomic deprivation should be designed to further investigate the increased incidence in areas of relatively high social deprivation, and to identify any modifiable risk factors.

To our knowledge, no previous study has reported the incidence of provoked seizures or seizure mimics with regard to socioeconomic status. Increased incidence of provoked seizures in areas of higher socioeconomic deprivation could be related to a higher prevalence of excessive alcohol intake and binge drinking in areas of relative socioeconomic deprivation.[23] Similarly, risk factors for other causes of provoked seizures, such as acute cerebrovascular accidents,[24] are more prevalent in areas of socioeconomic deprivation. Provoked seizures are associated with significant morbidity and mortality[25] and addressing risk factors for their development should be part of health policy.

The epidemiology of seizure mimics is not well studied. Our results demonstrate the highest incidence of seizures mimics in the most deprived quintile of the population, although a trend was not apparent. Seizure mimics represent a diverse group of disorders including vasovagal syncope, behavioural episodes, movement disorders and functional neurological disorders. Therefore, it is

difficult to explain this trend with a unifying explanation. Rather, this may reflect the increased morbidity across multiple different diseases which has been described in areas of socioeconomic deprivation[24, 26, 27] with higher presentation to medical services.

A major strength of our study is the use of the 2016 Pobal HP Deprivation Index[19] which provides a multidomain, multivariable R.D.I. as a continuous variable based on registered address which has been used to investigate the effect of socioeconomic status on survival in renal dialysis patients[28] and renal transplant patients[29] in Ireland. Area-level measures similar to the R.D.I. used in our study have been reported when investigating the association between epilepsy and socioeconomic deprivation in different geographic areas, specifically the Carstairs Index,[7] the Welsh Index for Multiple Deprivation[5] and the Townsend Index.[2, 9] The 2016 Pobal HP Deprivation Index uses more variables than other indices. Furthermore, it aims to assess lack of opportunity as a marker of socially deprivation, which is particularly relevant in rural communities thus allowing comparison of deprivation across the geographic area studied which includes both urban and rural communities.

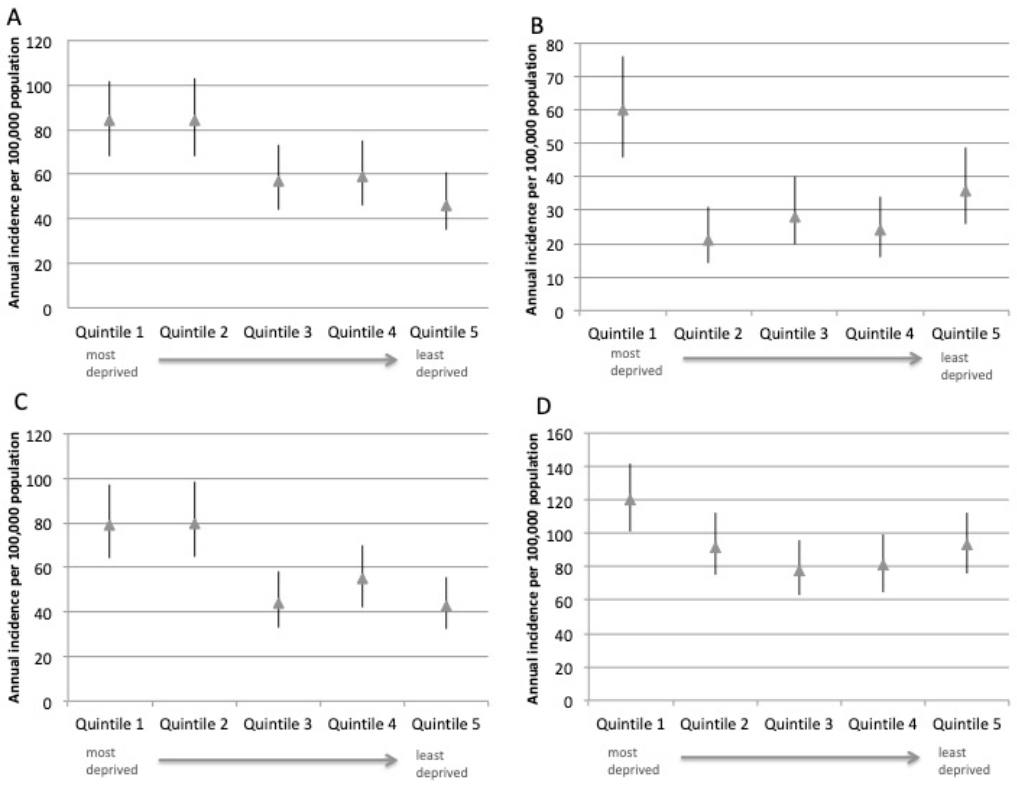
Area-level measures of deprivation as used in this study have potential weaknesses. They do not measure individual level deprivation and cannot account for the fact that an individual may live in an area of relative deprivation, but may not themselves be socially deprived. However, our results are concordant with prospective incidence studies which assessed socioeconomic deprivation on an individual level.[8, 11] The major limitation of our study is the lack of participant-level data from individual cases which would have allowed examination of individual level socioeconomic deprivation and relevant or potentially modifiable risk factors.

Taken together, our study suggests that the increased incidence of seizure disorders in socially deprived areas is multifactorial and not explained solely by either family history or environmental causes. Detailed prospective studies are needed to identify modifiable risk factors. The increased incidence of epilepsy

and seizure disorders in these areas should be reflected in greater access to diagnostic and treatment resources which, unfortunately, is not often the case in socially deprived areas.

4.6 Figures

Figure 4.1 The annual incidence of first unprovoked seizures (A), first provoked seizures (B), new diagnosis of epilepsy (C) and seizure mimics (D) in the most deprived quintile (1) compared to the least deprived quintile (5) of the defined geographic area during the calendar year 2017.



4.7 Tables

Table 4.1 Study population characteristics and mean Pobal 2016 HP Relative Deprivation Index (RDI) in Cork city and county and in each of the following diagnostic categories: first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics.[19] [20]

	Cork city and county		First unprovoked seizure	First provoked seizure	New diagnosis of epilepsy	Seizure mimics
Total persons	542,868		372	189	336	510
Mean age in years (5th and 95th centiles)	37.6		45.9 (2.2, 86.8)	52.6 (9.5, 85.6)	46.4 (2.9, 86.8)	41.8 (1.6, 84.5)
% male (n)	49.5 (268,675)		57.5 (214)	65.6 (124)	56.8 (191)	46.5 (237)
Median R.D.I. (5th, 95th centiles)	3.6 (-11.2, 12.1)		1.8 (-13.3, 9.8)	3.4 (-15.9, 12.1)	1.3 (-15.6, 9.6)	3.4 (-14.9, 12.1)
Quintile						
1 (most deprived)	n	108,753	90	61	85	131
	% male (n)	49.4 (53,726)	67.8 (61)	60.7 (39)	68.2 (n=58)	38.2 (50)
	Mean age in years (5th and 95th centiles)		43.7 (2.5, 86.6)	53.4 (20.2, 85.2)	43.9 (2.4, 87.4)	44.6 (1.8, 86.5)
	Median R.D.I. (5th, 95th centiles)	-5.6 (-18.1, -2.6)	-6.3 (-20.0, -2.5)	-8.0 (-19.8, -2.5)	-8.0 (-20.0, -2.6)	-8.0 (-20.0, -3.0)
2	n	108,396	91	23	87	100
	% male (n)	49.5 (53,682)	48.4 (44)	60.9 (14)	48.3 (42)	52 (52)
	Mean age in years (5th and 95th centiles)		50.5 (3.0, 85.9)	57 (18.7, 100.2)	50.5 (4.2, 85.2)	40.7 (1.1, 81.5)
	Median R.D.I. (5th, 95th centiles)	-0.1 (-2.2, 1.7)	-0.3 (-2.2, 1.6)	0.7 (-2.0, 1.8)	-0.3 (-2.2, 1.6)	0.1 (-2.2, 1.8)
3	n	108,604	62	31	48	85
	% male (n)	49.8 (54,117)	61.3 (38)	80.6 (25)	56.3 (27)	51.8 (44)
	Mean age in years (5th and 95th centiles)		42.7 (0.7, 89.0)	53.9 (1.3, 83.0)	44.9 (0.8, 89.5)	40.2 (1.3, 85.6)
	Median R.D.I. (5th, 95th centiles)	3.7 (2.3, 4.9)	3.7 (2.8, 5.1)	3.6 (2.4, 5.0)	3.7 (2.1, 5.1)	3.7 (2.2, 5.1)

[19] The R.D.I. of all Electoral Divisions (El.D.s) in Cork city and county was ranked from most deprived to least deprived. The El.D.s were divided into five quintiles based on an average population of approximately 108,000 per quintile. Quintile 1 represents one fifth of the population living in the most deprived El.D.s and Quintile 5 representing the fifth of the population living in the least deprived El.D.s. The number of cases and mean R.D.I. in group is shown. Only definite and probable cases were included in each diagnostic category. Persons living in nursing homes, convents or whose registered address was a prison or homelss were not included in the sociodemographic analysis. For this reason, there were 14 persons with a first unprovoked seizure, 9 persons with a provoked seizure, 10 persons with a new diagnosis of epilepsy and 6 persons with a diagnosis of a seizure mimic who were not included in the quintiles of their respective diagnostic group.

[20] 95%CI= 95% confidence interval of the mean.

Tables 4.1 contd. Study population characteristics and mean Pobal 2016 HP Relative Deprivation Index (R.D.I.) in Cork city and county and in each of the following diagnostic categories: first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics

	Cork city and county		First unprovoked seizure	First provoked seizure	New diagnosis of epilepsy	Seizure mimics
Total persons	542,868		372	189	336	510
Mean age in years (5th and 95th centiles)	37.6		45.9 (2.2, 86.8)	52.6 (9.5, 85.6)	46.4 (2.9, 86.8)	41.8 (1.6, 84.5)
% male (n)	49.5 (268,675)		57.5 (214)	65.6 (124)	56.8 (191)	46.5 (237)
Median R.D.I. (5th, 95th centiles)	3.6 (-11.2, 12.1)		1.8 (-13.3, 9.8)	3.4 (-15.9, 12.1)	1.3 (-15.6, 9.6)	3.4 (-14.9, 12.1)
Quintile						
4	n	109,171	65	26	60	88
	% male (n)	49.3 (53,786)	53.8 35)	69.2 (18)	53.5 (32)	38.6 (34)
	Mean age in years (5th and 95th centiles)		41.5 (1.1, 90.5)	53.5 (9.4, 80.7)	43 (1.7, 91.4)	39.5 (0.9, 82.2)
	Median R.D.I. (5th, 95th centiles)	6.7 (5.4, 7.4)	6.6 (5.5, 7.3)	6.6 (5.4, 7.3)	6.5 (5.4, 7.4)	6.7 (5.3, 7.5)
5 (least deprived)	n	107,944	50	39	46	100
	% male (n)	49.4 (53,364)	60 (30)	61.5 (24)	58.7 (27)	54 (54)
	Mean age in years (5th and 95th centiles)		46.5 (5.7, 87.3)	47.1 (3.6, 82.4)	46.9 (7.3, 85.5)	42.2 (1.6, 84.7)
	Median R.D.I. (5th, 95th .entiles)	9.5 (7.8, 12.8)	9.2 (7.8, 12.1)	9.2 (7.7, 12.1)	9.2 (7.8, 12.3)	9.7 (8.0, 12.1)

Table 4.2 Annual incidence of first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics per 100,000 population in the most deprived Electorial divisions (El.D.)s compared to the least deprived El.D.s.[21]

	Study population	First unprovoked seizures		First provoked seizures		New diagnosis of epilepsy		Seizure mimics	
Quintile	n	n	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)
1 (most deprived)	108,753	90	82.8 (66.9, 101.2) IR=1.79 (1.26, 2.52), p<0.001	61	56.1 (43.3, 71.6) IR=1.55 (1.04, 2.32), p<0.05	85	78.2 (62.8, 96.2) IR=1.83 (1.28, 2.62), p<0.001	131	120.5 (101.1, 142.4) IR=1.30 (1.00, 1.69), p<0.05
2	108,396	91	83.9 (68.0, 102.6) IR= 1.81 (1.28, 2.56), p<0.001	23	21.2 (13.8, 31.3) IR=0.59 (0.35, 0.98), p<0.05	87	80.3 (64.7, 98.5) IR=1.88 (1.32, 2.69), p<0.001	100	92.2 (75.5, 111.7) IR=1.00 (0.75, 1.31), p=0.98
3	108,604	62	57.1 (44.2, 72.7) IR=1.23 (0.85, 1.79), p=0.27	31	28.5 (19.7, 40.0) IR=0.79 (0.49, 1.27), p=0.33	48	44.2 (32.9, 58.1) IR=1.03 (0.69, 1.55), p=0.88	85	78.3 (62.9, 96.3) IR=0.84 (0.63, 1.13), p=0.25
4	109,171	65	59.5 (46.3, 75.4) IR=1.28 (0.89, 1.86), p=0.18	26	23.8 (15.9, 34.4) IR=0.66 (0.40, 1.08), p=0.10	60	55.0 (42.3, 70.2) IR=1.29 (0.88, 1.89), p=0.19	88	80.6 (65.0, 98.8) IR=0.87 (0.65, 1.16), p=0.34
5 (least deprived)	107,944	50	46.3 (34.8, 60.6) Reference	39	36.1 (26.1, 48.9) Reference	46	42.6 (31.6, 56.3) Reference	100	92.6 (75.8, 112.2) Reference

[21] IR=incidence ratio; 95%CI= 95% confidence intervals.

Table 4.3 The annual incidence of first unprovoked seizures, new diagnosis of epilepsy and seizure mimics per 100,000 population in those 0 to 14 years of age and in those 15 years of age and older in the most deprived EI.D.s compared to the least deprived EI.D.s.[22]

Persons <15 years old	Study population	First unprovoked seizure		New diagnosis of epilepsy		Seizure mimics	
Quintile	n	n	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)
1 (most deprived)	20, 341	20	98.3 (61.8, 149.1) IR=1.91 (0.91, 3.98), p=0.08	21	103.2 (65.6, 155.1) IR=2.20 (1.04, 4.68), p<0.05	18	88.5 (54.1, 137.1) IR=0.90 (0.48, 1.690) p=0.74
2	22,862	19	83.1 (51.5, 127.3) IR=1.61 (0.77, 3.89), p=0.20	14	61.2 (33.9, 100.3) IR=1.31 (0.58, 2.94), p=0.52	24	105.0 (68.8, 153.7) IR=1.07 (0.59, 1.91), p=0.83
3	24,233	19	78.4 (48.6, 120.15) IR=1.52 (0.72, 3.20), p=0.26	15	61.9 (36.0, 99.8) IR=1.32 (0.59, 2.94), p=0.49	21	86.7 (55.1, 130.2) IR=0.88 (0.48, 1.61), p=0.68
4	24,761	20	80.8 (50.7, 122.5) IR=1.57 (0.75, 3.27), p=0.23	18	72.7 (44.4, 112.6) IR=1.55 (0.72, 3.36), p=0.26	20	80.8 (50.7, 122.5) IR=0.82 (0.45, 1.51), p=0.53
5 (least deprived)	21,334	11	51.6 (27.1, 89.6) Reference	10	46.9 (23.8, 83.5) Reference	21	98.4 (62.6, 147.9) Reference
Persons ≥ 15 years old	Study population	First unprovoked seizure		New diagnosis of epilepsy		Seizure mimics	
Quintile	n	n	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)
1 (most deprived)	88,412	70	79.2 (62.2, 99.4) IR=1.76 (1.19, 2.60), p<0.01	64	72.4 (56.2, 91.8) IR=1.74 (1.16, 2.62), p<0.01	113	127.8 (105.8, 153.1) IR=1.40 (1.05, 1.87), p<0.05
2	85,534	72	84.2 (66.4, 105.4) IR=1.87 (1.27, 2.76), p<0.01	73	85.3 (67.4, 106.7) IR=2.05 (1.38, 3.06), p<0.001	76	88.8 (70.5, 110.6) IR=0.97 (0.71, 1.33), p=0.87
3	84,371	43	51.0 (37.4, 68.0) IR=1.13 (0.74, 1.75), p=0.57	33	39.1 (27.4, 54.3) IR=0.94 (0.59, 1.51), p=0.80	64	75.9 (58.9, 96.2) IR=0.83, (0.60, 1.16), p=0.27
4	84,410	45	53.3 (39.4, 70.7) IR=1.18 (0.77, 1.82), p=0.44	42	49.8 (36.3, 66.6) IR=1.20 (0.77, 1.87), p=0.43	68	80.6 (63.1, 101.5) IR=0.88 (0.64, 1.22) p=0.45
5 (least deprived)	86,610	39	45 (32.5, 60.9) Reference	36	41.6 (29.6, 56.9) Reference	79	91.2 (72.7, 113.1) Reference

[22] IR=incidence ratio; 95%CI= 95% confidence intervals.

Table 4.4 The annual incidence of new diagnosis of epilepsy of structural, genetic or unknown aetiology per 100,000 population in the most deprived El.D.s compared to the least deprived El.D.s.[23] [24]

	Study population	Structural		Genetic		Unknown	
Quintile	n	n	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)
1 (most deprived)	108,753	47	43.2 (32.1, 57.0) IR=1.73 (1.08, 2.78), p<0.05	10	9.2 (4.7, 16.4) IR=1.98 (0.68, 5.81), p=0.20	26	23.9 (16.0, 34.5) IR=2.15 (1.08, 4.26), p<0.05
2	108,396	44	40.6 (29.9, 54) IR=1.62 (1.00, 2.62), p<0.05	11	10.1 (5.3, 17.6) IR=2.19 (0.76, 6.30), p=0.14	27	24.9 (16.8, 35.7) IR=2.24 (1.13, 4.42), p<0.05
3	108,604	26	23.9 (16, 34.6) IR=0.96 (0.55, 1.64), p=0.87	6	5.5 (2.2, 11.5) IR=1.19 (0.36, 3.90), p=0.77	16	14.7 (8.7, 23.4) IR=1.32 (0.63, 2.80), p=0.46
4	109,171	31	28.4 (19.6, 39.8) IR=1.13 (0.68, 1.90), p=0.63	7	6.4 (2.8, 12.7) IR=1.38 (0.44, 4.36), p=0.58	20	18.3 (11.5, 27.8) IR=1.64 (0.81, 3.37), p=0.17
5 (least deprived)	107,944	27	25.0 (16.8, 35.9) Reference	5	4.6 (1.7,10.3) Reference	12	11.1 (6.0, 19.2) Reference

[23] Due to very small numbers, those with an infectious aetiology and or other aetiology were not analysed (n=4 and n=7 across all quintiles, see Chapter 5).
[24] IR- incidence ratio; 95%CI= 95% confidence intervals.

Table 4.5 The proportion of cases of definite or probable new diagnosis of epilepsy with a specific risk factor documented on retrospective chart review in each of the five quintiles, based on relative socioeconomic deprivation, of the defined geographic population.

Unknown means the risk factor was unknown or undocumented.[25]

		Febrile seizures			C.N.S. infection			Developmental delay			Family history of epilepsy		
		n	%	%*	n	%	%*	n	%	%*	n	%	%*
Quintile 1 (most deprived)	Yes	11	13	19	1	1	2	11	13	13	14	17	24
	No	47	55	81	58	68	98	74	87	87	47	55	76
	Unknown	27	32		26	31		0	0		24	28	
Quintile 2	Yes	5	6	8	1	1	2	8	9	9	15	17	23
	No	55	63	92	61	70	98	76	88	91	49	56	77
	Unknown	27	31		25	29		3	3		23	27	
Quintile 3	Yes	3	6	9	1	2	3	9	19	19	7	15	19
	No	31	65	91	33	69	97	38	79	81	30	62	81
	Unknown	14	29		14	29		1	2		11	23	
Quintile 4	Yes	1	2	2	0	0	0	6	10	10	10	17	24
	No	41	68	98	45	75	100	53	88	90	32	53	76
	Unknown	18	30		15	25		1	2		18	30	
Quintile 5 (least deprived)	Yes	1	2	3	1	2	3	5	11	11	4	9	13
	No	28	61	97	29	62	97	40	87	91	27	59	87
	Unknown	17	37		16	35		1	2		15	32	
		Drug or alcohol abuse			Head injury			Cerebrovascular disease			Psychiatric illness		
		n	%	%*	n	%	%*	n	%	%*	n	%	%*
Quintile 1 (most deprived)	Yes	5	6	7	4	5	7	30	35	35	5	6	6
	No	72	85	93	54	63	93	55	65	65	80	94	94
	Unknown	8	9		27	32		0	0		0	0	
Quintile 2	Yes	9	10	11	3	3	5	34	40	40	6	7	7
	No	69	80	89	56	65	95	50	57	60	81	93	93
	Unknown	9	10		28	32		3	3		0	0	
Quintile 3	Yes	6	12	15	3	6	5	13	27	27	3	6	6
	No	35	73	85	56	63	95	35	73	73	45	94	94
	Unknown	7	15		28	31		0	0		0	0	
Quintile 4	Yes	2	3	4	3	2	9	19	32	33	7	12	12
	No	48	80	96	30	70	91	39	65	64	51	85	85
	Unknown	10	17		15	28		2	3		2	3	
Quintile 5 (least deprived)	Yes	5	11	14	1	6	9	14	30	30	1	2	2
	No	31	67	86	42	59	91	32	70	70	45	98	98
	Unknown	10	22		17	35		0	0		0	0	

[25] %* refers to percentage yes or no of those with a documented response.

4.8 References

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Chapter 5 Causes and classification of all first unprovoked seizures and newly-diagnosed epilepsy in a defined geographic area

In this chapter of my PhD thesis, I explore the aetiology of first unprovoked seizures and newly diagnosed epilepsy in Cork city and county, 2017, by applying and critically appraising updated I.L.A.E. guidelines and classification systems. This chapter of my PhD thesis will be submitted to *Epilepsia* journal as an original research article. Co-authors are Dr. Éilis J O'Reilly and Dr. Daniel Costello.

5.1 Abstract

Objective: The I.L.A.E. recently updated both the operational definition of epilepsy and the classifications of seizures and epilepsy incorporating aetiology into the classification framework. To date, these classifications have not been reported in any whole population incidence study of seizures and epilepsy where all incident cases were identified.

Methods: Using multiple overlapping methods of case ascertainment, we identified all first seizures, new diagnosis of epilepsy and seizure mimics occurring in a defined geographic area (population 542,868) between 1st January 2017 and 31st December 2017. The 2017 I.L.A.E. classification framework for seizures and epilepsy type and aetiology were applied to all definite and probable first unprovoked seizures and new diagnosis of epilepsy. Incidence was age-standardised to the Standard European Population.

Results: The annual incidence per 100,000 population was 44 for focal epilepsy (age standardized 56), 6.8 for generalized epilepsy (age standardized 6.9) and 10.9 for unclassified epilepsy (age standardized 11.4). As may be expected, generalized epilepsy was most often diagnosed in those less than 25 years of age. Focal epilepsy was diagnosed in all age groups, though its incidence significantly increased in those over 55 years of age. The most frequently diagnosed aetiology was structural (54%, n=182). The annual incidence per 100,000 population of new diagnosis of epilepsy was 71 in males and 53 in females (male:female incidence ratio=1.34 (95% CI 1.08-1.67). There was no statistically significant difference in the underlying causes of epilepsy between males and females. In 30% (n=102) of newly diagnosed epilepsy, the cause was not established.

Significance: We report on the causes of incident first seizures and epilepsy in accordance with recently updated I.L.A.E. definitions and classification systems. We report a higher proportion of structural aetiology than previous studies, which may reflect incorporation of imaging in aetiology classification. The updated I.L.A.E. classification systems are clinically useful and should be incorporated in future epidemiologic studies. Despite improved access to diagnostic testing the cause of a large fraction of unprovoked first seizures and new-onset epilepsy remains unknown.

5.2 Introduction

Epidemiologic studies are needed to understand the burden of epilepsy within a population and to set public health priorities.[1] Incidence studies offer insights into the causes (aetiology) and natural history of a disease and more detailed reporting of incidence studies, especially with regard to seizure and epilepsy type, aetiology and age group specific results, have been called for.[2]

In 2011, the International League Against Epilepsy (ILAE) commission on epidemiologic studies produced guidelines for the methodology and reporting of incidence and prevalence studies in epilepsy.[1] Furthermore, the ILAE updated its operational definition of epilepsy in 2014,[3] such that a person can be diagnosed with epilepsy following a single seizure, if it is estimated that they have an approximately 60% or greater risk of recurrent seizures within 10 years after the occurrence of a first seizure. Prior to that, the 1993 ILAE definition required a person to have two or more unprovoked seizures at least 24 hours apart.[4] We previously demonstrated that application of the 2014 operational definition of epilepsy to a population resulted in a greater than 50% increase in the reported incidence of epilepsy as compared to the 1993 definition,[5] mostly due to the application of the '60% rule'.

With regard to classification of seizure and epilepsy type, the majority of previously published whole population incidence studies have reported a preponderance of focal seizures.[6-10] However, this has not been a consistent finding and some studies have reported a higher incidence of generalized seizures.[11-13] Furthermore, seizure and epilepsy type may not be reported depending on the methodology used to ascertain cases, for example where incidence results are obtained from ICD coding databases.[14, 15] Similarly, epilepsy aetiology may be reported in limited detail, or not at all, depending on the detail of case assessment. Lastly, seizure and epilepsy classification may be erroneous or not possible in some clinical circumstances. Review of individual incident cases by experts will likely lead to more accurate classification of seizures and epilepsy and assessment of aetiology in an entire population. Studies of epilepsy causation will be influenced by the characteristics of the population under

review. For example, the age distribution, diversity of causes and severity of epilepsy among patients attending epilepsy clinics in academic medical centers may differ to those in primary care settings.[16]

In 2017, the ILAE updated the classification of seizure[17] and epilepsy types.[18] These classification systems are clinically very useful as they allow results of investigations such as M.R.I. and E.E.G to inform the classification of seizure and epilepsy type. In addition, they update the aetiologic classification of epilepsy based on improved understanding of the epilepsies and their underlying mechanisms. We report in detail the results of a whole population incidence study of first unprovoked seizures and new diagnosis of epilepsy in a defined geographic region employing the 2017 ILAE classifications of seizure[17] and epilepsy[18] type.

5.3 Methods

This study was carried out in the geographically defined area of Cork city and county, Ireland, with an estimated population of 542,868 adults and children based on national census data from 2016.[19] The area contains one large urban development which encompasses approximately one quarter of the total population (125,657 adults and children). The remaining population lives in smaller towns, villages or rural dwellings. The geographic area spans approximately 7,500 km^2. The Irish healthcare system consists of both public and private hospitals. Patients with a first seizure who seek medical attention may either self-present to the emergency department, or are referred to the emergency department or outpatients department by their general practitioner (G.P.).

5.3.1 Case ascertainment and classification

A detailed description of the epidemiologic protocol applied to this population has been previously published.[20] In brief, multiple over-lapping sources of case

ascertainment were applied to the geographically defined area from 1st January 2017 to 31st March 2018 in order to capture all cases of possible first seizures, new diagnosis of epilepsy and seizure mimics whose first interaction with medical service for the event occurred during the calendar year 2017. Case ascertainment utilized a combination of prospective and retrospective methods in both community and hospital settings. All patients who presented to medical services during the calendar year 2017 with a possible first seizure or new diagnosis of epilepsy whose address, as per the hospital based administrative system, was within the geographically defined area were included. In accordance with the I.L.A.E. epidemiologic guidelines,[1] neonatal seizures and febrile seizures were excluded. Cases with inadequate or unclear documentation were classified as indeterminate (n=66, 5%). Epileptic seizures and epilepsy were defined according to the I.L.A.E. operational definitions.[3, 21] Provoked seizures[22] were identified as a specific sub-cohort, and were separated from first unprovoked seizures and epilepsy during analysis.

Following identification of a potential case, the medical chart and investigations of the patient were reviewed and validated first-hand. In particular, review of the documented medical history, E.E.G. findings and imaging was conducted by the study team (D.C. and E.M.) in each patient. In accordance with the I.L.A.E. epidemiologic study guidelines,[1] the probability that an event was a seizure or not, was defined as either a definite, probable or possible seizure, based on the evidence available. Cases who initially had a working diagnosis of seizure as judged by a first-line decision-maker (for example, an emergency department physician, G.P. or advanced paramedic), but who were ultimately determined not to have had a seizure (by an epileptologist, senior neurologist or senior physician), were classified as 'seizure mimics' and not included in this analysis (except as a comparator).

The 2014 I.L.A.E. operational definition of epilepsy[3] outlines that if, following a single unprovoked seizure, a person has an estimated approximate 60% or greater risk of recurrent seizures over the next ten years, they can be diagnosed with epilepsy. Definite, probable and possible single unprovoked seizures were

classified as definite, probable or possible epilepsy, respectively, if one or more of the following risk factors were identified: persons with a structural or remote symptomatic aetiology and/or epileptiform abnormality on E.E.G.[23-25] adults with a significant structural brain imaging abnormality,[24, 26, 27] neurodegenerative dementia,[28] or extensive small vessel disease with juxtacortical lesions.[29] Patients with two or more seizures were also classified as epilepsy. This classification was independent of whether the treating physician had commenced them on an antiepileptic drug (A.E.D.) or not. Patients with mild-to-moderate small vessel disease without juxtacortical lesions, other non-specific findings or normal investigations were classified as having had a single unprovoked seizure.

For all definite and probable first seizures and new diagnosis of epilepsy, the 2017 I.L.A.E. classification system for seizure[17] and epilepsy[18] type were applied. Cases were therefore classified as having focal onset, generalized onset or unknown onset seizures and epilepsy. Particular attention was paid to seizure semiology, where available and documented. In many patients, a focal epilepsy syndrome was inferred from the presence of focal E.E.G. or focal structural injury on brain imaging. For all definite and probable cases of epilepsy, aetiology was classified according to the 2017 I.L.A.E. classification framework[18] as structural, genetic, immune, infectious, metabolic or unknown. Structural aetiology was further subtyped into microvascular, macrovascular, neurodegenerative, or other specific epileptogenic structural abnormalities. Some patients were determined to have both microvascular disease and neurodegenerative disease as potential underlying aetiology for their epilepsy. For clarity of reporting these cases were classified as neurodegenerative aetiology. Patients with underlying developmental abnormalities, such as autism or intellectual disability, of unspecified or unknown cause were classified as unknown.

Potential risk factors for epilepsy were identified where possible during the retrospective chart review. Risk factors identified included a family history of epilepsy, history of febrile seizures, head injury, central nervous system infection, cerebrovascular disease or a history of psychiatric illness. It was noted

whether the case was prescribed a medication with psychoactive effects. Cases in whom there was no documentation in the medical notes as to the presence or absence of a specific risk factor were coded as unknown.

5.3.2 Statistical analysis

Demographic data are presented as median and interquartile range (I.Q.R.). Demographic data from All Ireland Census 2016[19] was used to calculate age-group and gender specific incidence. Age-standardisation was performed by comparison to the 2013 European Standard Population.[30] Eurostat does not provide information on certain age groups, for example, those aged under 1 year. Therefore, for age standardization, 5-year age groups were used. Gender-specific incidence was compared using incidence ratios. To compare epilepsy aetiology between genders, Pearsons Chi Square test was performed. The prevalence of risk factors among definite and probable cases of epilepsy (n=336) compared to seizure mimics (n=510) were analysed using logistic regression. Although they do not represent the general population, the group of persons diagnosed with a seizure mimic was chosen for comparison as they were collected simultaneously to those who were diagnosed with definite or probable epilepsy and therefore similar data on risk factor prevalence was available. Similar data from the general population in the defined geographic area is not publically available. However, those with a diagnosis of definite or probable epilepsy had a greater proportion of males (n=191, 57%) compared to seizures mimics (n=237, 46%) and an older median age at presentation (53 years compared to 42 years). For the risk factors of drug or alcohol abuse and mental illness, only persons over age 15 were included in analysis as there were no persons under this age with a positive history. The risk factor of mental illness includes persons with a history of bipolar affective disorder, schizophrenia, depression or anxiety. Results were determined to be significant for $p<0.05$. Statistics were performed using SPSS version 26 for Mac.

5.3.3 Ethics

The study protocol was approved by the University College Cork Clinical Research Ethics Committee (Appendix 1). Following ascertainment, data was de-identified and anonymised prior to analysis and storage. We report our results in adherence with S.T.R.O.N.D.[30] guidelines.

5.4 Results

5.4.1 Age and gender specific annual incidence of seizure and epilepsy type according to the 2017 I.L.A.E. classification

An overview of included cases and demographic data of cases of first unprovoked seizure (n=523) and new diagnosis of epilepsy (n=419) are shown in Figure 5.1. Only definite and probable cases [71% (n=372) and 80% (n=336), respectively] were included in further analysis of incidence, aetiology, risk factors and seizure and epilepsy type.

The annual incidence of all first unprovoked seizures was 69 per 100,000 (age-standardised 83). The annual incidence per 100,000 of all first unprovoked seizures was 80 in males and 58 in females:incidence ratio (IR)=1.38 (95% CI 1.13-1.70). The annual incidence of first single unprovoked seizure with an estimated less than 60% risk of recurrence was 12 per 100,000 (age-standardised 14). In males, the annual incidence per 100,000 of first single unprovoked seizure with less than 60% risk of recurrence was 16, in females it was 9 [IR=1.71 (95%CI 1.04-2.81)]. The annual incidence of new diagnosis of epilepsy was 62 per 100,000 (age standardized 74). The annual incidence per 100,000 of new diagnosis of epilepsy among males was 71 as opposed to females 53 [IR=1.34 (95% CI 1.08-1.69)].

The crude age-specific annual incidence of all definite and probable first unprovoked seizures at low risk of recurrence, first unprovoked seizures at high

risk of recurrence, persons who had more than one seizure and all definite and probable new diagnosis of epilepsy is shown in Figure 5.2. The gender-specific annual incidence in each group is shown in Figure 5.3 (A-D). A bimodal age-specific incidence is evident in both males and females with a single seizure and an estimated <60% risk of recurrence and in those with >2 seizures. However, the incidence of those with a single seizure and an estimated =>60% risk of recurrence appears more stable in youth, begins to increase over the age of 45 and then increases significantly over the age of 65 years. The increased incidence in males compared to females is evident in those less than 35 years of age and converges in older age-groups across all groups.

Of all definite or probable first unprovoked seizures, 64.5% (n=240) were classified as focal onset, 8.5 % (n= 32) were generalized onset and 17% (n=63) were classified as unknown onset tonic clonic seizures. The remaining first unprovoked seizures were unclassified (10%, n=37), supplemental Figure 5.1(A). The annual incidence of first unprovoked focal seizure was 44 (age-standardised 57), first generalized onset seizures was 5.8 (age standardized 6.1), unknown onset tonic clonic 11.6 (age standardized 12) and unclassified seizures was 6.8 (age standardized 8.8) per 100,000 population.

Of all new definite and probable new diagnosis of epilepsy, 71% (n=240) were classified as focal, 11% (n=37) were classified as generalized and 18% (n=59) were unclassified, supplemental 5.1(B). The incidence of focal epilepsy per 100,000 population was 44 (age standardized 56), generalized epilepsy 6.8 (age standardized 6.9) and unclassified was 10.9 (age standardized 11.4). As may be expected, generalized epilepsy was most often diagnosed in those less than 25 years of age. Focal epilepsy was the most common classification in all age groups, except those 15-24 years of age, see Figure 5.4. The incidence of focal epilepsy was highest in older age groups. Specifically the annual incidence of focal epilepsy in those aged 0-64 years was 26 per 100,000 and the annual incidence in those 65 years of age and older was 157 per 100,000. Therefore the increasing annual incidence of epilepsy seen in older age-groups, resulting in the bimodal age-specific distribution (Figure 5.3, D), is driven mainly by focal epilepsy,

whereas epilepsy of unknown classification remains relatively flat across all age groups and generalised epilepsy is diagnosed almost exclusively in those under 25 unders of age.

5.4.2 Investigations

For all definite and probable first unprovoked seizure (n=372), 88% (n=328) of cases had at least one form of imaging, either C.T. or M.R.I., and 38% (n=140) had both. Of those who did not have any imaging (n=44), 34% (n=15) had a diagnosis of an intellectual disability or advanced dementia, 23% (n=10) were diagnosed with childhood genetic generalised epilepsy, 14% (n=6) had recent brain imaging for another indication and had a known structural abnormality, 11%(n=5) were children with a single unprovoked seizure, 11% (n=5) were assessed in the private sector and it was unclear if they had imaging or not and 7% (n=3) did not have imaging for another reason. Sixty-one percent (n=226) had a routine E.E.G., 4% (n=16) had a sleep deprived E.E.G. and 2% (n=7) had video E.E.G. during the study period.

For persons diagnosed with definite or probable epilepsy (n=336), 87% (n=292) had at least one form of brain imaging, either C.T. or M.R.I., and 38% (n=127) had both. Of those who did not have any brain imaging, 38% (n=17) had a diagnosis of an intellectual disability or advanced dementia, 23% (n=10) were diagnosed with childhood genetic generalised epilepsy, 16% (n=7) had recent prior brain imaging with a known structural aetiology, 14% (n=6) were seen in the private sector and it was not clear if they had imaging or not and 9% (n=4) did not have imaging for another reason. Sixty-seven percent (n=226) underwent an E.E.G. study. Of those who had such investigations, 42% (n=81) had a normal or non-specific finding on C.T., 43%(n=96) had a normal or non-specific M.R.I. and 45% (n=102) had a normal E.E.G. Six percent (n=22) had a second E.E.G., 4.5% (n=15) had a sleep deprived E.E.G., and 2% (n=6) had video E.E.G. during the data collection period. Supplemental Table 5.1 and 5.2 demonstrates the results of

investigations for definite and probable first unprovoked seizures and new diagnosis of epilepsy.

In cases of definite or probable first unprovoked seizure (n=372) where the C.T. brain scan was normal (n=82), 82% (n=67) of cases went on to have an M.R.I. brain. In 16% (n=11) of these, an imaging finding associated with seizures was identified. These included two cases of hippocampal sclerosis, two areas of focal gliosis involving the cortex, two areas of abnormal T2 hyperintensity involving cortex, one arteriovenous malformation, one cavernoma, one focal cortical dysplasia, one limbic encephalitis, and one developmental abnormality.

5.4.3 Aetiology

Almost one third of cases of new diagnosis of epilepsy were classified as unknown aetiology (30%, n=102). Structural lesion(s) represented the most frequently diagnosed aetiology (54%, n=182). There was no statistically significant difference in epilepsy aetiology between males and females, see Table 5.1. Genetic aetiology was diagnosed most often in those less than 34 years of age, whereas structural aetiology was more frequently diagnosed in older age groups, see Figure 5.5.

5.4.4 Risk factors

As outlined in section 5.3.1, males were at significantly increased risk of all first unprovoked seizures, single seizures with less than 60% risk of recurrence and new diagnosis of epilepsy in (p=0.0019, p=0.0307 and p=0.007, respectively). Those 65 years of age and older were significantly more likely to be diagnosed with a first unprovoked seizure [IR=3.58 (95%CI 2.89-4.42, p=0.000)], a single seizure with a less than 60% risk of recurrence [IR=1.83 (95%CI 1.03-3.25, p=0.0359)] and of new diagnosis of epilepsy [IR=3.71 (95%CI 2.98-4.64, p=0.0000)] compared to those less than 65 years of age. However, the trend was

not linear with increased incidence in those less than 5 years of age compared to those betweeen 5 to 65 years.

Patients with a family history of epilepsy were more likely to be diagnosed with epilepsy than with a seizure mimic [OR 1.97 (CI 1.25-3.10; p=0.003,)] compared to those without a family history of epilepsy. Cases with a history of febrile seizures were statistically significantly more likely to be diagnosed with epilepsy than with a seizure mimic [OR 4.91 (CI 1.95-12.37, p=0.0007)] compared to those without a history of febrile seizures. Cases with a history of developmental delay were significantly more likely to be diagnosed with epilepsy than a seizure mimic [OR 2.59 (CI 1.56 to 4.32, p=0.0003)] compared to those without a history of developmental delay. Finally, compared to those cases with no history of cerebrovascular disease, cases with a history of macrovascular disease and microvascular disease were more likely to be diagnosed with epilepsy than with a seizure mimic [OR 4.25 (CI 2.18-8.29, p=0.00002) and OR 1.59 (CI 1.13-2.23, p=0.007), respectively].

There was no difference between cases diagnosed with epilepsy compared to cases diagnosed with a seizure mimic in persons with a history of alcohol or drug abuse, major mental illness or use of psychoactive medication. Cases with a history of head injury were three times [OR 3.1, (95% CI 1.2-7.6, p=0.015)] more likely to be diagnosed with epilepsy than with a seizure mimic. However, those with a diagnosis of a seizure mimic were statistically significantly more likely to have an unknown or undocumented history of head injury (p=0.007) compared to those with a diagnosis of epilepsy. Similarly, those with a diagnosis of a seizure mimic were significantly more likely to have an unknown or undocumented history of central nervous system infection (p=0.002) compared to those with epilepsy. Supplemental Table 5.2 outlines the epilepsy associated risk factors in those cases with a definite or probable first unprovoked seizure or new diagnosis epilepsy.

5.5 Discussion

Incidence studies provide valuable insights into the aetiology of diseases within a population. However, due to the difficulty in identifying incident cohorts, few whole population incidence studies are performed, and there is a lack of detailed reporting of results of incidence studies.[2] The I.L.A.E. has recently revised and updated its classification system for seizure[17] and epilepsy types,[18] as well as epilepsy aetiology, taking into account advances in knowledge regarding the underlying mechanism of epilepsy. Using multiple methods to maximize case ascertainment and individual case analysis, we report the incidence of first unprovoked seizures and epilepsy in accordance with these updated classification systems and detailed analysis of seizure and epilepsy type, aetiology and risk factors. Individual case analysis of clinical history, E.E.G. and imaging results were combined to classify cases based on available evidence, as recommended in the I.L.A.E. classification systems.

Our results demonstrated a higher incidence of focal epilepsy compared to generalized epilepsy or epilepsy of unknown onset. The previous I.L.A.E. classification of partial versus generalized epilepsy has been applied to some previous whole population studies. The basic principles of the two classification systems are similar, though the updated version allows imaging results to inform the classification of epilepsy. The majority of previous whole population studies using the older I.L.A.E. classification system have reported a higher incidence of partial seizures,[6-9, 32] which is concordant with our finding of a higher incidence of focal onset seizures and focal epilepsy and reinforces the validity of our results. The detailed analysis of each individual case record in our study, as well as review of all their relevant investigations, reinforces the accuracy of our results. However, a number of previous studies report a higher incidence of generalized epilepsy compared to focal epilepsy.[11-13] These studies relied solely on a clinical description of the seizures for epilepsy classification. Therefore, persons with focal onset to bilateral tonic clonic seizures may have been incorrectly classified as generalized epilepsy. For example, Benn et al., in 2008[10] found that in 97% of seizures classified as generalized it could not be determined

if onset was generalized or focal. This highlights the clinical usefulness of the 2017 I.L.A.E. classification system[17] where 'unknown onset tonic clonic seizure' is a distinct classification term.

Similar to our results, a higher incidence of seizures and epilepsy in males compared to females has been reported previously.[7, 11, 13-15, 32-35] A single study reported a higher incidence in females than males.[12] However, this study utilized survey of households within clusters of villages in Tanzania as a single ascertainment method and the validity of results is unknown. It has been hypothesized that the higher incidence of epilepsy among males may be due to a higher incidence of structural aetiologies due to risk factors such as head injury. However, we found no significant difference in the subtype of epilepsy due to structural aetiology between males and females. Indeed, there was no significant difference between genders in any of the aetiological categories. This suggests that the apparent gender difference cannot be accounted for by a single aetiological explanation. In contrast to our results, a recent study from Iceland[9] reported no significant difference in incidence between males and females. This was a detailed, whole population study and so raises the possibility that gender-specific incidence may vary in different geographic areas.

With regard to aetiology, previous studies reported a higher proportion of epilepsy of unknown aetiology compared to our study, between 50 and 80%. [6, 9, 11, 32, 36, 37] We report a higher proportion of structural aetiology in our cases of definite and probable epilepsy. This may be attributed to improvement in epilepsy related M.R.I. imaging as well as incorporation of imaging into the 2017 classification system. It is worth noting that a significant proportion of our cases of structural aetiology were attributed to microvascular disease (n= 50, 15%). In cases in whom microvascular disease was determined to be the aetiology of epilepsy, the presence of juxtacortical white matter hyperintensities were specifically sought on M.R.I. imaging.[38] This was particularly relevant in cases who presented with a single unprovoked seizure and in whom it was estimated that there was an approximately 60% or greater risk of recurrent seizures. Persons with a single unprovoked seizure and minor or solely subcortical, deep

white matter hyperintensities were not labeled as epilepsy. With regard to other structural aetiologies of epilepsy diagnosed on M.R.I., our results are similar to Hakami et al., 2013[39] who found a potentially epileptogenic lesion in 28% (n=164) of new diagnosis of epilepsy attending a first seizure clinic compared to 31% (n=71) in our cohort..

With regard to persons who develop epilepsy in the setting of intellectual disability or autism, the 2017 aetiology classification outlines that the term 'symptomatic generalised' epilepsy should no longer be used. Though there may be a genetic aetiology underlying many of these cases, for the vast majority of cases, a specific genetic diagnosis is not made. It is difficult to know where to classify these cases within the confines of the updated system. For clarity of reporting we have included them as a subgroup within the unknown aetiology group, though future work on classification and aetiology of these specific cases is needed. Olafsson et al.,[9] applied the previous I.L.A.E. syndrome classification to their population and found that 27% of epilepsy fell into a non-specific category, whereas only 18% of our cases were unclassified. This probably reflects better diagnostic tools particularly M.R. imaging. In addition, it suggests that the updated I.L.A.E. guidelines for seizure and epilepsy type may be more practically applicable than previous guidelines and are useful when applied to population based studies.

Ten percent of definite and probable first unprovoked seizures who underwent brain imaging were diagnosed with a brain tumour. This is important to consider when assessing first seizures in an emergency department setting. Of those who had normal C.T. scan and went on the have a M.R.I. scan, 16% had an epileptogenic structural lesion on M.R. imaging which was not seen on the C.T. study. In some of these cases, the finding of an epilepsy associated abnormality led to an earlier diagnosis of epilepsy, initiation of appropriate treatment and monitoring. Of those with a definite or probable first seizure who had a routine E.E.G., approximately 40% (n=97) had a significant finding of either focal slowing, focal sharp waves, generalized discharges or a focal or generalized seizure. A very small percentage of cases in our cohort had a sleep deprived

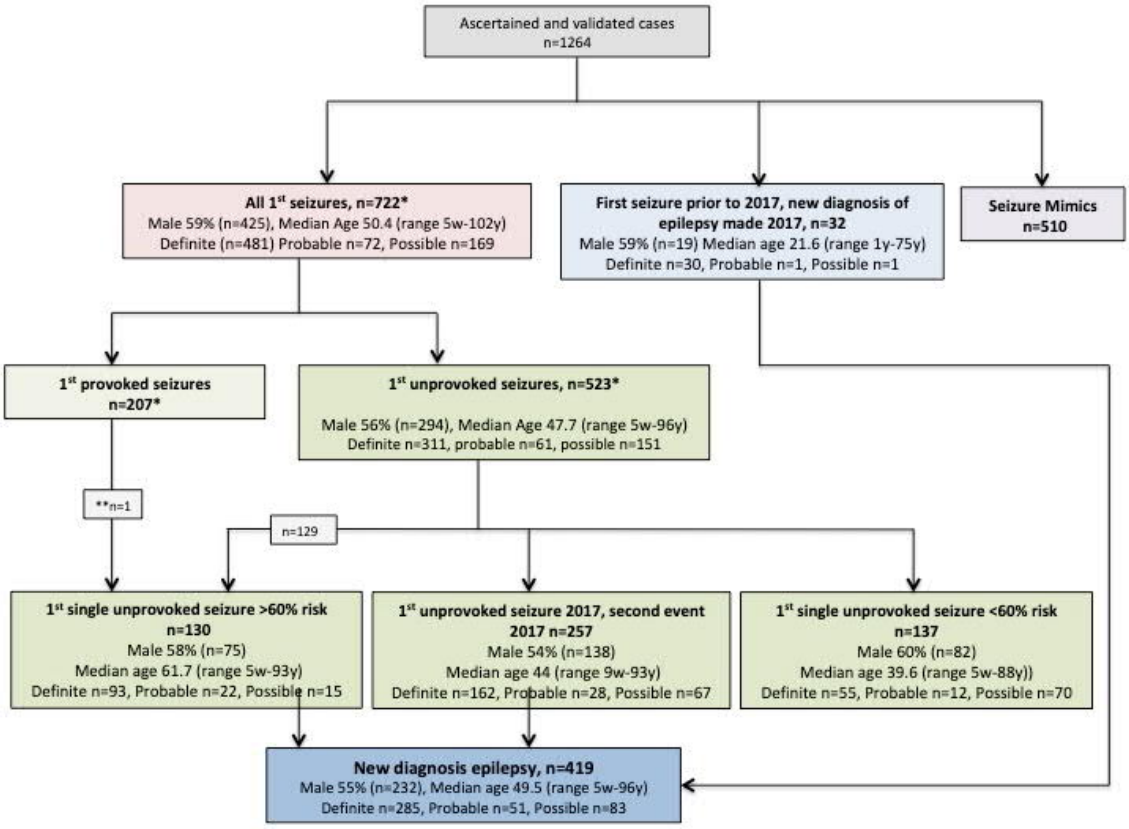
E.E.G. following normal routine E.E.G. and this may differ from practices elsewhere. Greater utilization of sleep deprived E.E.G at our service may further aid classification of epilepsy.

The majority of cases in our cohort either did not have specific risk factors, or did not have documentation of specific risk factors, for epilepsy. Cases who had a positive history of febrile seizures, developmental delay, cerebrovascular disease or a family history of epilepsy, were more likely to be diagnosed with definite or probable epilepsy than a seizure mimic. However, numbers were small and in all groups a significant proportion of cases did not have a documented history of whether a specific risk factor was present or not. One of the limitations of this study is that the case analysis was performed using routinely collected clinical data. Therefore, information on risk factors may not have been specifically asked or recorded. If a case was evaluated by a neurologist or an epileptologist, they may have been more likely to have epilepsy specific risk factors recorded. As such, cases diagnosed as seizure mimics were more likely to have an undocumented history of head injury or central nervous system infection compared to those diagnosed with epilepsy. Improved education and awareness of seizure risk factors among general and emergency department physicians may help to address this gap. Prospective studies with standardized risk factor assessment are needed to more accurately determine factors associated with seizure and epilepsy risk.

5.6 Figures

Figure 5.1 Overview of the case classification of all possible first presentations of seizures and new diagnosis of epilepsy within the defined geographic region during the calendar year 2017.

Cases in whom an alternate diagnosis was reached were classified as seizure mimics. [26]



[26] *Eight cases had both a first provoked and first unprovoked seizure during the study period. ** One case of a first provoked seizure was deemed to also be at significantly increase risk of recurrent seizures and was therefore also classified as epilepsy. w=weeks; y=year

Figure 5.2 Crude annual age-specific incidence per 100,000 population of all definite and probable first single unprovoked seizures with a <60% risk of recurrence (n=67), first single unprovoked seizures with a =>60% risk of recurrence (n=115), cases who had a history of 2 or more unprovoked seizures (n=221) and new diagnosis of epilepsy (n=336) within the defined geographic region during the calendar year 2017.

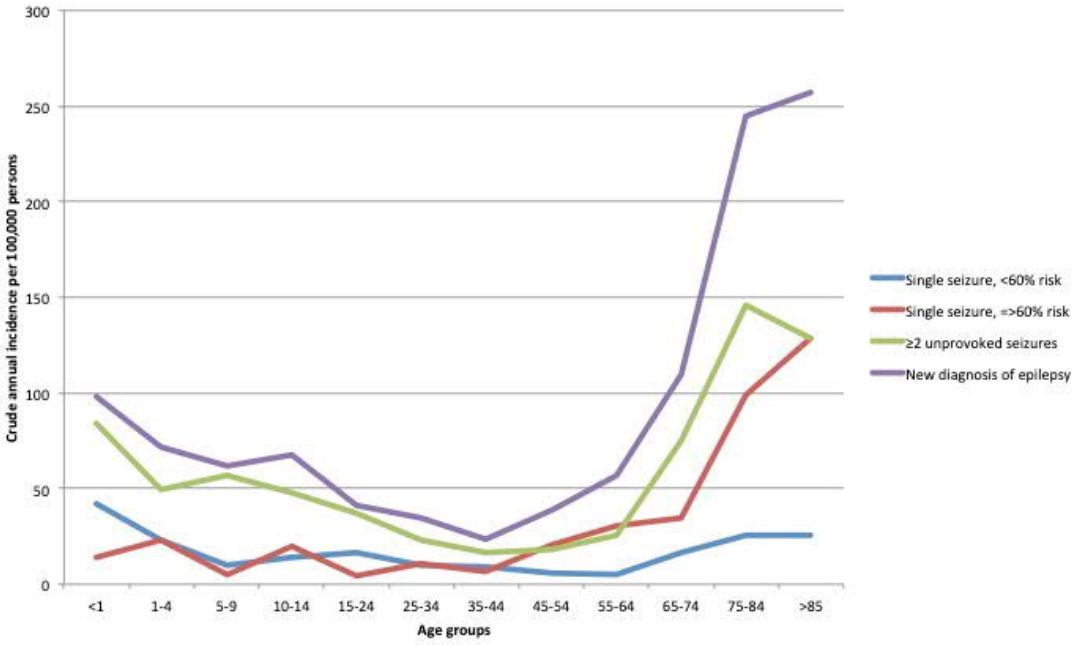


Figure 5.3 Crude annual gender and age-specific incidence of all definite and probable (A) first single unprovoked seizures with a <60% risk of recurrence (n=67), (B) first single unprovoked seizures with a =>60% risk of recurrence (n=115), (C) cases who had a history of 2 or more unprovoked seizures (n=221) and (D) new diagnosis of epilepsy (n=336) within the defined geographic region during the calendar year 2017.

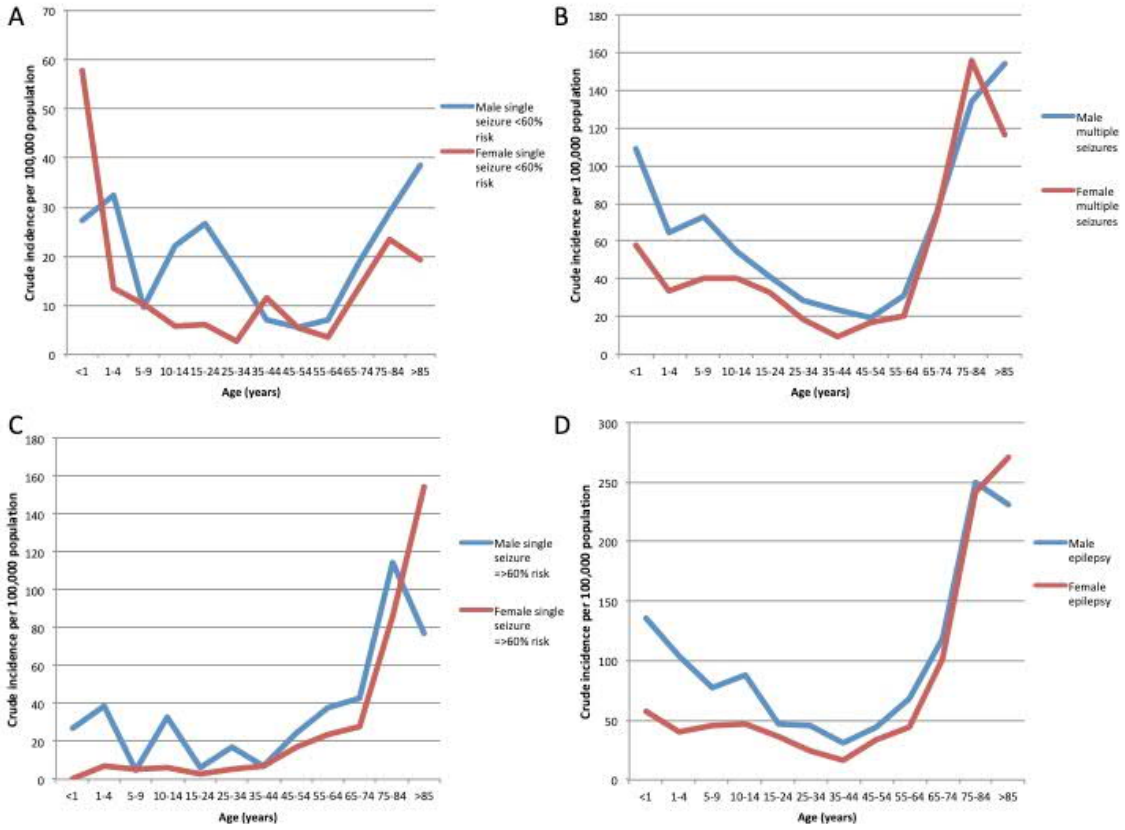


Figure 5.4 Crude annual incidence per 100,000 population of all definite and probable new diagnosis of focal epilepsy (n=240), generalized epilepsy (n=37) and unclassified epilepsy (n=59) within the defined geographic region during the calendar year 2017.

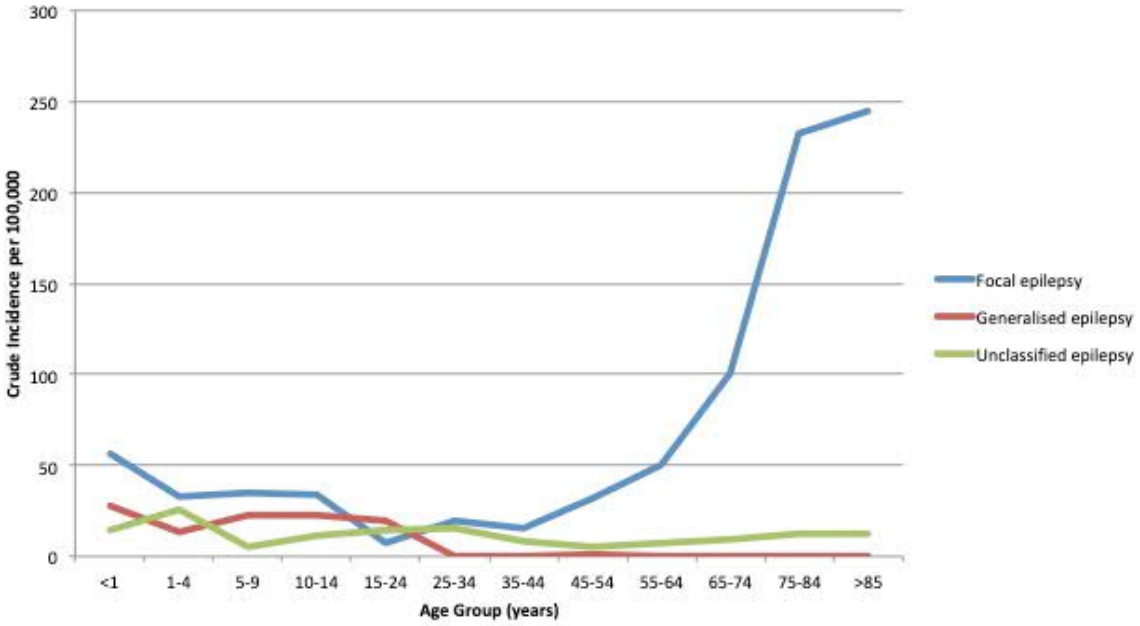
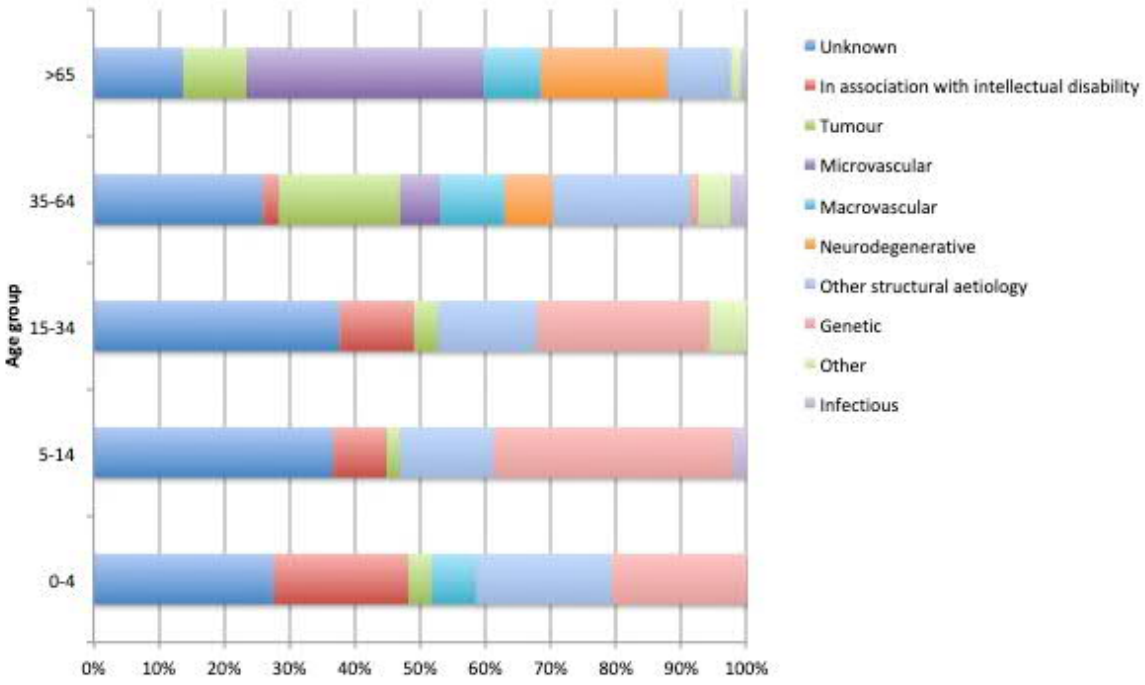
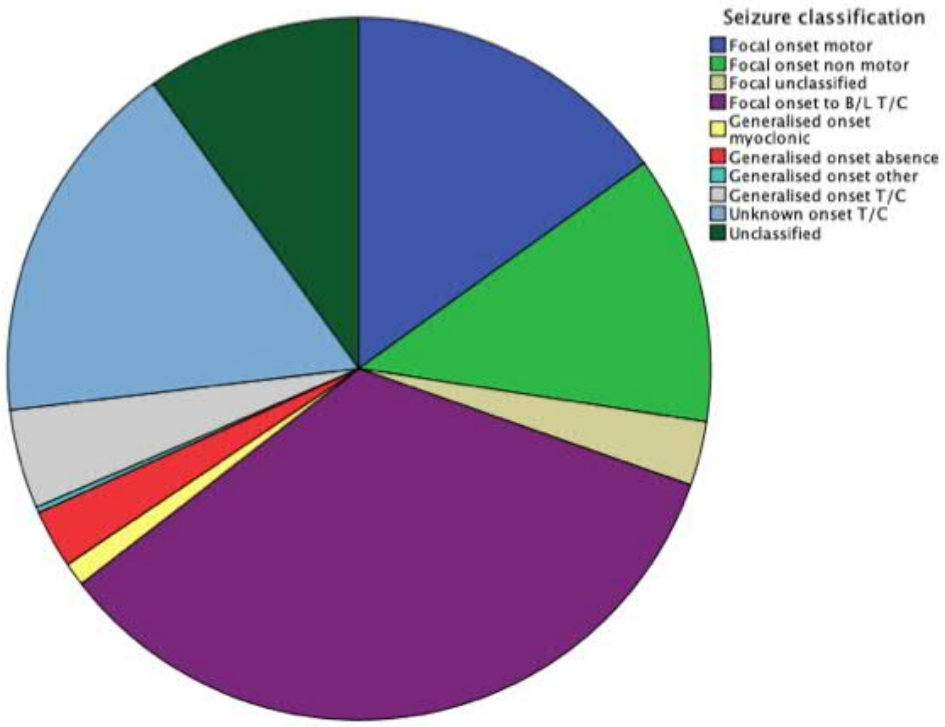


Figure 5.5 Age-group specific aetiology of all definite and probable new diagnosis of epilepsy (n=336) within the defined geographic region during the calendar year 2017.

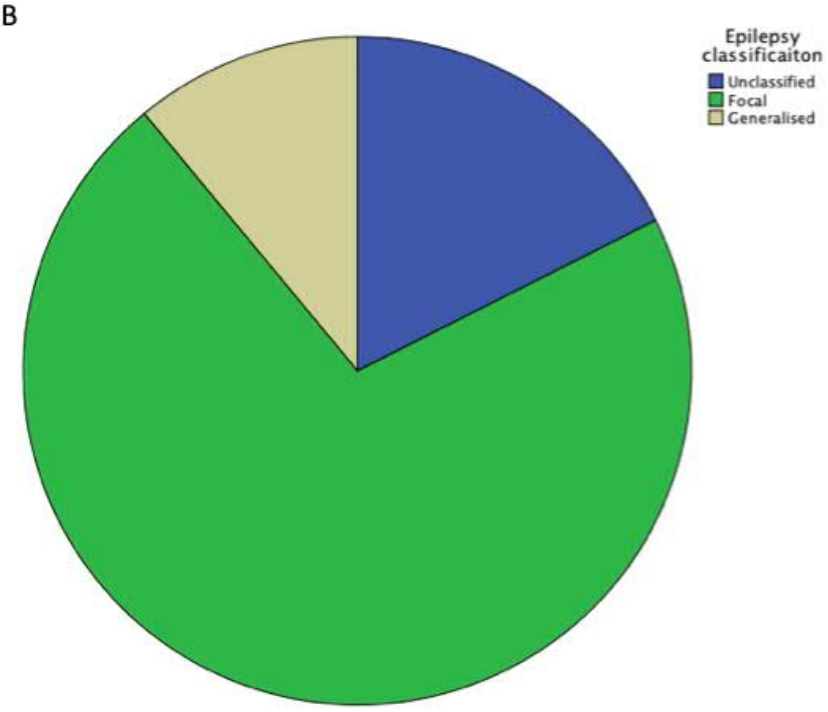


Supplemental Figure 5.1 Pie charts representing the proportion of focal onset, generalised onset and unclassified seizures for all definite and probable first unprovoked seizures (n=372, A) and the proportion of focal, generalised and unknown classification of all definite and probable epilepsy (n=336, B).

A



B



5.7 Tables

Table 5.1 Aetiology of all definite and probable new diagnosis of epilepsy in the defined geographic region during the calendar year 2017.

Aetiology of all definite and probable new diagnosis of epilepsy during the calendar year 2017 (n=337)		Total (n)	%	Male (n)	%	Female (n)	%	p
Unknown		102	30	61	32	41	28	0.5
	Idiopathic	84	25	48	25	36	25	-
	In association with underlying intellectual disability (formerly symptomatic generalized)	18	5	13	7	5	3	-
Structural		182	54	106	55	76	53	0.6
	Microvascular disease	50	15	26	14	24	17	-
	Brain tumour	31	9	18	9	13	9	-
	Neurodegenerative disease	30	9	16	8	14	10	-
	Macrovascular disease	21	6	14	7	7	5	-
	Other structural cause	20	6	14	7	6	4	-
	Focal gliosis	11	3	7	4	4	3	-
	Cavernoma	6	2	3	2	3	2	-
	Multiple sclerosis	4	1	1	<1	3	2	-
	Cerebral palsy	3	<1	3	2	0		-
	Focal cortical dysplasia	2	<1	1	<1	1	<1	-
	Polymicrogyria	2	<1	1	<1	1	<1	-
	Hippocampal sclerosis	2	<1	2	1	0		-
Genetic		39	12	17	9	22	15	0.07
	Genetic generalized (formerly idiopathic)	32	10	16	8	16	11	0.4
	Gene specific	7	2	1	<1	6	4	-
Other		9	3	6	3	3	2	-
	Subarachnoid haemorrhage	2	<1	0		2	1	-
	Chronic alcohol abuse	2	<1	2	1	0		-
	Post traumatic	2	<1	2	1	0		-
	NMDA receptor encephalitis	1	<1	1	<1	0		-
	L.O.M.E.D.S.	1	<1	1	<1	0		-
	C.N.S. Vasculitis	1	<1			1	<1	-
Infectious	Post Encephalitis	4	1	1	<1	3	2	-
Total		336	100	191	100	145	100	

Supplemental Table 5.1 Results of CT, MRI and EEG for all definite and probable first unprovoked seizure (A) and new diagnosis of epilepsy (B) in the defined geographic region during the calendar year 2017

Other epilepsy risk factor on imaging include areas of focal gliosis from previous head injury or surgery, subdural hygroma with mass effect, subependymal calcifications. Non specific finding refers to global or focal atrophy, arachnoid cysts and boney lesions without mass effect. Other EEG findings refer to sharply contoured delta or non-specific features for which follow up EEG may have been recommended.

A. Results of investigations of all definite and probable first unprovoked seizure (n=372)		n	%
CT			
	No CT	155	41.7
	Normal	82	22
	White matter hypodensities	49	13.2
	Tumour	22	5.8
	Non specific finding	22	6
	Other epilepsy risk factor	19	5.1
	Macrovascular disease	16	4.3
	Acute haemorrhage	5	1.4
	Unknown	2	0.5
	Total	372	100
MRI			
	No MRI	116	31.2
	Normal	98	26.3
	White matter hyperintensities	57	15.3
	Other epilepsy risk factor	43	11.6
	Tumour	21	5.6
	Non specific findings	18	4.8
	Macrovascular disease	7	1.9
	Acute haemorrhage	3	0.8
	Not tolerated	1	0.3
	Unknown	8	2.1
	Total	372	100
EEG			
	No EEG	124	33.3
	Normal	121	32.5
	Focal sharp waves	40	10.8
	Focal slowing	27	7.3
	Generalised discharges	20	5.4
	Generalised slowing	15	4
	Other	12	3.2
	Focal onset seizure	8	2.2
	Generalised onset seizure	2	0.5
	Unknown	3	0.8
	Total	372	100

B. Results of investigations of all definite and probable new diagnosis of epilepsy (n=336)		N	%
CT			
	No CT	144	42.9
	Normal	64	19
	White matter hypodensities	47	14
	Tumour	22	6.5
	Non specific finding	17	5.1
	Other epilepsy risk factor	18	5.3
	Macrovascular disease	17	5.1
	Acute haemorrhage	5	1.5
	Unknown	2	0.6
	Total	336	100
MRI			
	No MRI	104	31
	Normal	83	24.7
	White matter hyperintensities	54	16
	Other epilepsy risk factor	42	12.5
	Tumour	21	6.3
	Non specific findings	13	3.8
	Macrovascular disease	8	2.4
	Acute haemorrhage	3	0.9
	Not tolerated	2	0.6
	Unknown	6	1.8
	Total	336	100
EEG			
	No EEG	107	31.8
	Normal	102	30.4
	Focal sharp waves	44	13.1
	Focal slowing	23	6.8
	Generalised discharges	24	7.1
	Generalised slowing	15	4.5
	Other	10	3
	Focal onset seizure	6	1.8
	Generalised onset seizure	2	0.6
	Unknown	3	0.9
	Total	336	100

Supplemental Table 5.2 Proportion of cases of definite and probable first unprovoked seizure (n=372) and new diagnosis of epilepsy n=(336) with a positive or negative documented history of a specific risk factor.

Unknown cases refer to cases in which there was no documentation regarding the specific risk factor, therefore it was either not known or not documented.

		First unprovoked seizure		New diagnosis of epilepsy	
Risk factor		n	%	n	%
Family history epilepsy	Yes	57	15	50	15
	No	203	55	187	56
	Unknown	112	30	99	29
Febrile seizures	Yes	22	6	21	6
	No	221	59	204	61
	Unknown	129	35	111	33
Drug or alcohol abuse	Yes	27	7	29	78
	No	287	77	260	8
	Unknown	58	16	47	14
Head injury	Yes	14	4	16	5
	No	230	62	210	62
	Unknown	128	34	110	33
C.N.S. infection	Yes	4	1	4	1
	No	245	66	228	68
	Unknown	123	33	110	31
Developmental delay	Yes	38	10	42	12
	No	325	88	288	86
	Unknown	9	2	6	2
Cerebrovascular disease	Macrovascular	30	8	31	9
	Microvascular	87	24	83	25
	No	247	66	216	64
	Unknown	8	2	6	2
Mental Illness	Yes	30	8	24	7
	No	337	91	309	92
	Unknown	5	1	3	1
Psychiatric medications	Yes	69	18	59	17
	No	291	78	268	80
	Unknown	12	3	9	3
Total		372		336	

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Chapter 6 The incidence and aetiology of acute symptomatic seizures in a defined geographic area

In this chapter of my PhD thesis, I present and analyse the incidence and aetiology of acute symptomatic seizures in Cork city and county, 2017, and critically discuss the I.L.A.E. classification of such seizures.

This chapter of my PhD thesis will be submitted to *Epilepsia* journal as an original research article. Co-authors are Dr. Éilis O'Reilly and Dr. Daniel Costello.

6.1 Abstract

Objects: Acute symptomatic seizures represent a significant proportion of all seizures occurring within a population, yet whole population studies investigating their incidence and aetiology are lacking.
Methods: Using multiple overlapping methods of case ascertainment, we identified all first acute symptomatic seizures in a defined geographic area (population 542,868) between 1st January 2017 and 31st December 2017. I.L.A.E. guidelines for case definition and aetiology were applied. Incidence was age-standardised to the Standard European Population.
Results: The annual incidence of all first acute symptomatic seizure was 35 per 100,000 population (95%CI 30-40; age-standardised incidence 42). Males were significantly more likely to present with an acute symptomatic seizure compared to females [incidence ratio 1.95; 95% CI (1.44-2.63) p<0.001]. Alcohol and/or illicit drug use represented the most common aetiology and accounted for the majority of the gender difference. Twelve percent (n=23) of acute symptomatic seizures occurred in patients who were metabolically unwell, yet did not fulfill the current I.L.A.E. criteria for acute symptomatic seizure.
Significance: Acute symptomatic seizures, especially those due to alcohol and illicit drug use, represent a significant burden to the health care system of the population studied and public health initiatives are needed to address their occurrence. Further studies are needed to define the limits of metabolic disturbance which classify a seizure as acute symptomatic in aetiology.

6.2 Introduction

Acute symptomatic (or 'provoked') seizures are defined as seizures occurring in close temporal relationship with an acute central nervous system insult which may be metabolic, toxic, structural, infectious or due to inflammation.[1] Evidence suggests that acute symptomatic seizures have a different prognosis to unprovoked seizures with a lower risk of subsequent recurrent unprovoked seizures.[2] Therefore, acute symptomatic seizures are distinguished from epilepsy, which is characterized by an enduring predisposition to recurrent unprovoked seizures,[3] both clinically and in epidemiologic studies.[4]

The International League Against Epilepsy (I.L.A.E.) has released guidelines for the definition of acute symptomatic seizures in epidemiologic studies with regard to the nature of the insult and the temporal relationship between the acute insult and the occurrence of a seizure.[1, 4] However, due to limited published research in the area, the absolute values of cutoffs for metabolic disturbance are based on the extreme end of abnormalities. Furthermore, certain commonly encountered metabolic disturbances, such as sepsis and multiorgan dysfunction, are not addressed in these guidelines. In clinical practice, it is not uncommon for neurologists to encounter patients where seizures seem to be a consequence of transient acute illness and where the long-term risk of recurrent seizures are intuitively felt to be low. These situations often do not qualify as acute symptomatic seizures according to the strict I.L.A.E. definition.

There are a limited number of whole population incidence studies investigating acute symptomatic seizures. Annual incidence estimates range from 16 to 35 per 100,000 population per year[5-10] and only one study from Greece[11] has been published since the 2011 updated I.L.A.E. epidemiologic guidelines.[1, 4] Reported aetiology of acute symptomatic seizures is likely to vary depending on age structure, environmental and cultural factors associated with the geographic area and therefore information from previously unstudied populations are of value.

As in all epidemiologic studies, methodology of case ascertainment will affect completeness of case ascertainment, validity of results and level of case-specific details available. Acute symptomatic seizures may be particularly difficult to ascertain from an epidemiologic point of view as such seizures are seldom indexed as a diagnosis, making studies relying on seizure hospital coding databases inefficient, and an electroencephalographic evaluation may not be warranted.[1] We previously published a detailed epidemiologic protocol, adherent to I.L.A.E. guidelines, for maximal ascertainment of all first seizures and new diagnosis of epilepsy within a defined population[12] and herein report the details of acute symptomatic seizures within the population.

6.3 Methods

6.3.1 Base population

This study was carried out in the geographically defined area of Cork city and county, Ireland, with an estimated population of 542,868, predominantly Caucasian (93%), adults and children based on national census data from 2016.[13] The area contains one large urban development which encompasses approximately one quarter of the total population (125,657 adults and children). The remaining population lives in smaller towns, villages or rural dwellings. The geographic area spans approximately 7,500 km^2. We report our results in adherence with S.T.R.O.N.D. guidelines.[14]

6.3.2 Case ascertainment and classification

A detailed description of the epidemiologic protocol applied to this population has been previously published.[12] In brief, multiple over-lapping sources of case ascertainment were applied to the geographically defined area from 1st January 2017 to 31st March 2018 in order to capture all cases of possible first seizure, new diagnosis of epilepsy and seizure mimics whose first interaction with

medical services for the event occurred during the calendar year 2017. Case ascertainment relied on a combination of prospective and retrospective methods in both community and hospital settings. All patients who presented to medical services during the calendar year 2017 with a possible first seizure or new diagnosis of epilepsy whose address, as per the hospital based administrative system, was within the geographically defined area were included. In accordance with the I.L.A.E. epidemiologic guidelines, neonatal seizures and febrile seizures were excluded. Cases with inadequate or unclear documentation were classified as indeterminate. Acute symptomatic seizures were identified as a specific sub-cohort, and were separated from first unprovoked seizures and epilepsy for the pruposes of analysis.

Acute symptomatic seizures were defined according to the I.L.A.E. recommendations.[1] In addition, we deliberately included cases where a first epileptic seizure occurred in persons who were systemically unwell in the setting of clearly documented sepsis, usually with associated metabolic derangement, severe enough to require hospitalisation (n=23, 12%).

Following the identification of a potential case, the medical-chart and investigations of the patient were reviewed first-hand. In accordance with the I.L.A.E. epidemiologic study guidelines,[4] the probability that an event was an acute symptomatic seizure was defined as either a definite, probable or possible based on the evidence available, as follows:
i) Definite: with primary documentation of (a) an epileptic seizure with evidence that this was provoked by any acute medical condition or transient brain disorder or (b) documentation of diagnosis of an acute symptomatic seizure by someone with appropriate specialised training in the recognition of seizures/epilepsy.
ii) Probable: with other sources of information indicating the likelihood that criterion (a) or (b) above is met.
iii) Possible: where primary or other sources of information suggest a possibility of an acute symptomatic seizure but neither (a) or (b) above is met. Possible acute symptomatic seizures are defined as an event of which a seizure was one of

a number of plausible differential diagnoses, but of which it was not possible to determine which was the most likely.

6.3.3 Statistical analysis

Demographic data are presented as median and interquartile range (I.Q.R.). Only definite and probable cases of acute symptomatic seizures were included in the calculation of incidence and analysis of aetiology (91%, n=189). Demographic data from All Ireland Census 2016[13] was used to calculate annual age-group and sex-specific incidence per 100,000 population. Ninety-five percent confidence intervals (95% CI) were calculated for annual incidence. Age-standardisation was performed by comparison to the 2013 European Standard Population.[15] Eurostat does not provide information on certain age groups, for example, those aged less than one. Therefore, for age standardisation 5-year age groups were used. Incidence ratios and 95% CI were used to compare gender-specific incidence. Incidence ratios were deemed to be statistically significant for $p<0.05$. Statistical analyses were performed using SPSS version 24 for Mac.

6.3.4 Standard protocol approvals

The study protocol was approved by the University College Cork Clinical Ethics Research Committee (Appendix 1). Following ascertainment, the data were anonymised prior to analysis and storage.

6.4 Results

Two hundred and seven first diagnosis of acute symptomatic seizure were identified during the study period, of which 86% (n=178) were classified as definite, 5% (n=11) as probable and 9% (n=18) as possible, see Table 6.1. Males represented 66% of all first acute symptomatic seizures (n=137). Median age of onset was 55.4 years (I.Q.R. 37.9 years; range 7 weeks - 102 years). Seizure was

the presenting symptom and reason for admission to hospital in 53% (n=101) of cases. The median length of stay in hospital was 6 days (I.Q.R. 16; range 1-259 days).

The annual incidence of first acute symptomatic seizure was 35 per 100,000 population (95%CI: 30-40; age-standardised incidence 42). The unadjusted incidence of acute symptomatic seizures in males was 46 per 100,000 (95% CI 39-55) and in females was 24 (95%: CI 19-30), incidence ratio 1.95 (95% CI (1.44-2.63, p<0.001). The higher incidence in men was apparent in all age groups except for those over 85, see Figure 6.1.

Following exclusion of cases due to sepsis (n=23, 12%), as this is not specifically mentioned in the I.L.A.E. definition[1] of acute symptomatic seizure, the annual incidence was attenuated from 35 to 31 per 100,000 population (95% CI 26-36); age-standardized incidence attenuated from 42 to 35. The male to female ratio was not materially changed [2.00 (95%CI: (1.45-2.77), p<0.001].

The aetiology of all definite and probable first acute symptomatic seizures ascertained in the defined geographic area during the calendar year 2017 are shown in Table 6.2. The crude incidence of first acute symptomatic seizures due to alcohol and/or illicit drug use was 15.47 per 100,000 (95%CI 12.34- 19.15). The incidence ratio of acute symptomatic seizures due to alcohol and/or illicit drug use in males compared to females was 3.27 (95%CI 1.98-5.39, p<0.001). The crude incidence of acute symptomatic seizure from all other aetiology was 19.34 per 100,000 (95%CI 15.82-23.41). The incidence ratio of acute symptomatic seizure due to all other aetiology in males compared to females was 1.36 (95%CI 0.92-2.00, p=0.12). The aetiology according to age group at event are shown in Figure 6.2. Alcohol and illicit drugs were the most common aetiologies among those aged 15-64 years. Stroke and metabolic disturbance were the most common aetiologies in those 65 years of age and older.

Of those diagnosed with a definite or probable first acute symptomatic seizure, 14% (n=27) died during the hospital stay. Of these cases, 85% (n=23) had been

admitted to hospital for reasons other than a seizure. The median age of those who died during hospital admission was 77 years (I.Q.R. 15, range 42- 91).

6.4.1 Discussion

Fastidious case ascertainment and validation is necessary to identify first acute symptomatic seizures and to differentiate them from unprovoked seizures and epilepsy.[1] There is a relative lack of published studies investigating this cohort of 'first seizure' patients. Using up-to-date I.L.A.E. epidemiologic definitions[1] and guidelines[4] and a rigorous study protocol,[12] we report an annual incidence of first acute symptomatic seizures of 35 per 100,000, a significantly increased incidence in males and a significant associated mortality.

Using sophisticated coded medical record data and analysing all first acute symptomatic seizures in persons over 1 month of age in Rochester, United States of America from 1935 to 1984, Annegers et al., 1995[6] reported age-adjusted annual incidence similar to this study at 35 per 100,000. Age-adjusted annual incidence from 1955-1984, when case ascertainment was estimated to be more complete, was reported at 39 per 100,000. Interestingly, the authors note some changes in aetiology over this time period, for example eclampsia was a common aetiology before 1965 and was less common after that time, presumably due to improvements in obstetric medicine. Indeed, head trauma and central nervous sytem infection were more common aetiologies in their population compared to ours, representing 16% and 15% of acute symptomatic seizures, respectively. Therefore, decreased incidence in acute symptomatic seizures of certain aetiologies in our population may be attenuated by increased incidence of other aetiologies such as alcohol and drug misuse, resulting in a convergence of the two estimates.

Other whole population studies used a limited number of case ascertainment methods and report annual incidence ranging from 16 to 29 per 100,000 population (see Table 6.3). It is worth noting that the definition of an acute

symptomatic seizure used by Loiseau et al., in 1990[5] when reporting a crude annual incidence of 29 per 100,000 in all persons over 2 months of age in Gironde, France, between 1984-85, is quite different to that which is currently recommended. For example, epileptic seizures occurring in the context of dementia were included as acute symptomatic, therefore it is difficult to directly compare results. Similar to our study, most previously reported studies report a higher incidence in males than females with the exception of Stranjalis et al., 2009[10] who reported a higher incidence of epileptic seizures in females than in males in northwest Greece, though it is unclear if there was a difference in gender in the subgroup of acute symptomatic seizures.[27]

Almost half (45%) of all recorded provoked seizures were related to alcohol (38%) and/or illicit drug use (7%). The remaining cases were largely attributed to intercurrent acute brain injury or irritation. Similar to our study, alcohol has been reported as the most common aetiology in studies from Geneva,[7] Martinique Island[8] and La Reunion.[9] Although aetiology of acute symptomatic seizures is likely to vary depending on cultural and environmental factors, it is clear that alcohol and illicit drug use represent a significant burden to healthcare services in many populations and therefore significant public health resources are required to address these issues. Our results demonstrate that alcohol and illicit drugs were more common in males than females and accounted for most of the higher incidence in men, which, to our knowledge, has not been previously reported. Unlike previous studies from Rochester,[6] Martinique Island[8] and La Reunion,[9] trauma resulting in acute symptomatic seizures did not feature as prominently in our population. It is possible that improvements over time in road safety accounts for this difference.

We report significant inpatient mortality in those with acute symptomatic seizures. It is interesting to note that the majority of these patients were not primarily admitted for seizures. Therefore, an acute symptomatic seizure may be

[27] I have emailed Dr. Alamano, correspnding author of this paper, on 1st May 2020, to establish if there was a difference in gender-specific indidence of acute symptomatic seizures in their population. He has not yet been able to clarify.

a marker of systemic illness and frailty in this group of patients and this area deserves more study. Increased mortality associated with acute symptomatic seizures was also reported by Hesdorffer et al., 2009[2] who reported persons diagnosed with an acute symptomatic seizure due to stroke, traumatic brain injury or central nervous system infection were 8.9 times more likely to die within 30 days compared to those with an unprovoked seizure.

There is a lack of published research regarding what degree of metabolic disturbance constitutes an acute symptomatic seizure. Intuitively, it is defined by the fact that, were the provoking factor to be removed, the seizure would not have occurred. It is in this context that 12% (n=23) of our cases (n=189) were judged to have an acute symptomatic seizure provoked by sepsis and systemic inflammatory markers, though this is not specifically outlined within the I.L.A.E. criteria[1] at present. For clarity of reporting and to allow comparison between future studies we have separated these cases as a specific cohort. Further study on the risk of recurrence within this cohort will help further clarify this issue and advance the definition of an acute symptomatic seizure.

Acute symptomatic seizures differ to epilepsy in terms of prognosis and recurrence. However they represent a significant proportion of all first seizures which occur within a population.[24] We previously reported an annual incidence of all first seizures in this defined population of 102 per 100,000 population, therefore acute symptomatic seizures represent approximately one third of all first seizures and those due to alcohol and/or illicit drug misuse account for almost one sixth of all ‘first seizure’ patients. Public health and health care initiatives may aim to reduce their incidence and associated morbidity and mortality by targeting modifiable aetiologies.

6.5 Figures

Figure 6.1 Crude sex and age-group specific annual incidence of acute symptomatic seizures in the defined geographic area during the calendar year 2017.

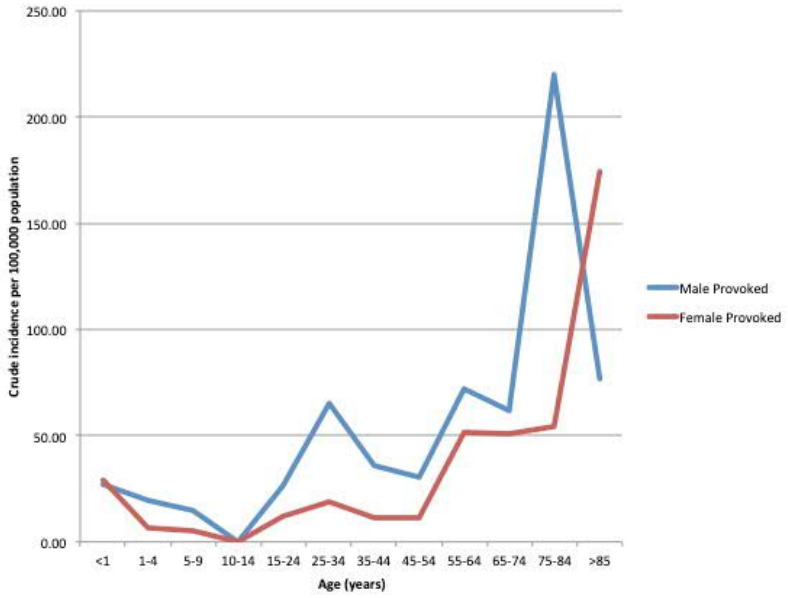
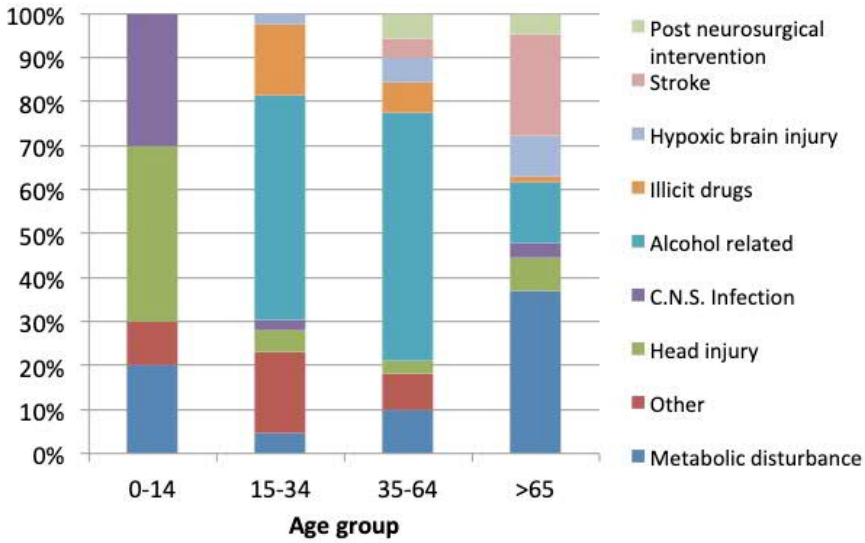


Figure 6.2 Age-group specific aetiology of acute symptomatic seizures in the defined geographic area during the calendar year 2017.



6.6 Tables

Table 6.1 Demographic data of cases of definite, probable and possible acute symptomatic seizures in the defined geographic area during the calendar year 2017.

	Age group	Definite	Probable	Possible	Total
Male	<15	7	0	1	8
	15-34	29	3	4	36
	35-64	46	1	7	54
	>65	35	3	1	39
Female	<15	3	0	0	3
	15-34	11	0	2	13
	35-64	23	1	0	24
	>65	24	3	3	30
Total		178	11	18	207

Table 6.2 Aetiology of all definite and probable provoked seizures (n=189) in the defined geographic area during the calendar year 2017. [28]

Aetiology		M	F	Total	%
Alcohol related		54	17	71	38
	Alcohol withdrawal	*32*	*13*	*45*	*24*
	Alcohol +illicit drugs	*10*	*2*	*12*	*7*
	Alcohol intoxication	*8*	*2*	*10*	*5*
	Alcohol + metabolic disturbance	*4*	*0*	*4*	*2*
Illicit drugs (without alcohol)		10	3	13	7
Metabolic disturbance		19	16	35	17
	Sepsis	*14*	*9*	*23*	*12*
	Hyponatraemia	*2*	*4*	*6*	*3*
	Hypoglycaemia	*3*	*2*	*5*	*2*
	H.H.S.	*0*	*1*	*1*	*<1*
Stroke		10	8	18	10
	Ischaemic stroke	*5*	*2*	*7*	*4*
	Intracerebral haemorrhage	*4*	*3*	*7*	*4*
	Subarachnoid haemorrhage	*0*	*3*	*3*	*<2*
	Subdural haemorrhage	*1*	*0*	*1*	*<1*
Head injury		9	4	13	7
Hypoxic brain injury		6	5	11	6
Post neurosurgical intervention		7	0	7	4
C.N.S. infection		3	3	6	3
Other		6	9	15	8
Total		124	65	189	100

[28] C.N.S.= central nervous system; H.H.S.- Hyperglycaemic Hyperosmolar State; M=male; F=female. Other includes 4 cases of seizures provoked by prescribed medications, 2 cases of posterior reversible encephalopathy syndrome, 2 cases of hypertensive crisis without evidence of posterior reversible encephalopathy syndrome on imaging, 2 cases of C.N.S. autoimmune inflammation, 1 case following anaesthesia, 1 case following blockage of a ventroperitoneal shunt, 1 case following cerebral venous sinus thrombosis, 1 case of eclampsia and 1 case following intrathecal administration of methotrexate.

Table 6.3 Comparison of previously published whole population studies investigating the incidence of acute symptomatic seizures with regard to case ascertainment, aetiology and gender differences. [29]

Study	Loiseau et al., 1990[5]	Annegers 1995[6]	Jallon 1997[7]	Jallon 1999[8]	Mignard et al., 2009[9]	Stranjalis et al., 2009[10]	Verentzioti et al., 2017[11]	Current study
Geographic area (population)	Gironde, France (1,128,164)	Rochester, U.S.A. (c.40,000)	Geneva, Switzerland (384,657)	Martinique island (383,596	La Reunion Island (763,204)	Corfu, Greece (113,479)	Lesvos, Greece (86,436)	Cork, Ireland, (542, 868)
Years cases occurred	1984-85	1935-84	1991-92	1994-95	2004-05	2004-05	2010-11	2017
Population included	All persons > 2 months old	All persons >1 month old	Whole population	All persons >1 month old	All persons >1 month old	Whole population	All persons >1 month old	All persons >1 month old
Case ascertainment methodology								
Radiology database								X
E.E.G. database	X		X		X			X
E.D.				X			X	X
Neurologists and Paediatricians	X		X	X	X	X	X	X
Other hospital specialists								X
R.A.S.C.								X
Clinical Nurse Specialist								X
G.P. survey				X			X	X
Residential care survey								X
Patient Advocacy Group								X
Social security foundation						X		
Hospital medical record data		X					X	

[29] E.D.= emergency department; E.E.G.= electroencephalogram; G.P.= General Practitioner; R.A.S.C= Rapid Access Seizure Clinic; U.S.A.= United States of America.

Table 6.2 (contd.). Comparison of previously published whole population studies investigating the incidence of acute symptomatic seizures with regard to case ascertainment, aetiology and gender differences.[30]

Study	Loiseau et al., 1990[5]	Annegers 1995[6]	Jallon 1997[7]	Jallon 1999[8]	Mignard et al., 2009[9]	Stranjalis et al., 2009[10]	Verentzioti et al., 2017[11]	Current study
Geographic area (population)	Gironde, France (1,128,164)	Rochester, U.S.A. (c.40,000)	Geneva, Switzerland (384,657)	Martinique island (383,596)	La Reunion Island (763,204)	Corfu, Greece (113,479)	Lesvos, Greece (86,436)	Cork, Ireland, (542, 868)
Aetiology; three most common in order of incidence. (where available, prevalence or incidence of risk factor in geographic area)	C.V.D. (334)[16,31] Toxic (7)[17, 32] Infection	Trauma (701)[18,33] C.V.D (373)[19,34] Infection	Alcohol Toxic Stroke (143)[20,35]	Alcohol C.V.D. (160)[21,36] Trauma	Alcohol Trauma C.V.D. (587)[22,37]	C.V.D. (587)[22,7] Toxic Drugs	C.V.D. (587)[22,7] Metabolic Tumour	Alcohol Metabolic C.V.D. (193)[23,38]
Gender ratio	Not reported	M>F	M>F	M>F	M>F	Not reported	M>F	M>F
Annual incidence per 100,000 persons	29 (crude)	35 (age-adjusted to U.S.A.)	25.2 (age-adjusted to U.S.A.)	16.4 (age-adjusted to U.S.A.)	17.7 (crude)	27.3 (crude)	16.2	35

[30] C.V.D.= cerebrovascular disease; M=Male; F=Female; U.S.A.= United States of America.
[31] Crude annual stroke (ischemic and haemorrhagic) incidence per 100,000 inhabitants in Northen France, measured between 2008 and 2015.
[32] Past year prevalence of DSM-VI alcohol abuse per 1,000 population in France in 2001/2.
[33] Average annual incidence of all E.D. attendance for head injury (minor or major) per 100,000 population between 2007 and 2011 in the U.S.A.
[34] Crude annual incidence rate per 100,000 person-years in the U.S between 1987 to 2011 prospectively collected in persons aged 45-64 at study onset.
[35] Crude annual incidence of first ever ischemic stroke per 100,000 population in Geographically defined area of Swizerland in 2002-3.
[36] Population based crude annual incidence of first ever stroke per 100,000 persons of French African Caribbean ethnicity in Martinique Island, 1989-90
[37] Population based crude annual incidence of all strokes per 100,000 peron-years in Northern Greece in 2010-12.
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Chapter 7 Summary and future recommendations

7.1 Study overview

This thesis presents a detailed methodology, adherent to international guidelines[1] and definitions,[2-4] designed to maximize case ascertainment for investigation of the incidence of first seizures, new diagnosis of epilepsy and seizure mimics in a previously unstudied defined geographic area. The methodology reflects good epidemiologic practice and aims to avoid shortfalls in previously published studies which typically ascertained incident cases from limited sources. The published results[5] present the first international data on the effect of the updated 2014 I.L.A.E. definition of epilepsy[2] on whole population incidence of epilepsy. Furthermore, by applying I.L.A.E. classifications[3, 4] to individual cases, this thesis presents detailed data on the aetiology and classification of seizures and epilepsy within the studied population. Finally, this thesis provides further support to international evidence that relatively higher socioeconomic deprivation is associated with an increased incidence of seizures and epilepsy and presents novel data regarding the association with specific aetiologies of epilepsy and relative socioeconomic deprivation. In this chapter, a summary discussion of each individual chapter is presented, focusing on the strengths of the research, contribution of the findings to national and international published research and its potential limitations. Following this, recommended areas for future research are discussed and finally a conclusion for this research thesis is presented.

7.2 Application of recent international epidemiological guidelines to a prospective study of the incidence of first seizures, newly-diagnosed epilepsy and seizure mimics in a defined geographic region in Ireland

Analysis and interpretation of the epidemiologic data of this thesis are reliant on accurate, valid and reproducible methodology. Correspondingly, significant time and effort was invested in maximizing and validating case ascertainment methodology within the confines of our health care system. In general, previous studies rely on either coded medical record data, or more labour intensive data collection from clinical databases or clinician survey. The former method is somewhat less burdensome. However, it relies on accurately coded medical data with detail required for epidemiologic research. In Ireland, H.I.P.E. data has limited use in epidemiological studies because it only captures presentations to acute hospital settings and it does not differentiate between new and established diagnosis of epilepsy. In addition, data are not coded to allow classification of seizures or epilepsy by type or suspected aetiology. Following review of international literature, it was determined that dynamic, 'real world' ascertainment of cases would be necessary in our health care setting. Maximal case ascertainment was achieved by combining prospective and retrospective methods followed by cross-reference to a central database.

Based on clinical experience, it was anticipated that certain patients may not be captured by the more commonly used methods of ascertainment, such as E.E.G. and radiology database searches. For example, patients may not be ascertained from such methods if they were admitted for a systemic illness, or if they were known to be at high risk of a seizure, but were admitted for another reason, such as those undergoing a neurosurgical intervention. It was anticipated that these patients may not have specific investigations to diagnose their seizure and therefore contacting medical and surgical teams and C.N.S.s directly was incorporated into the methodology. Most previous studies do not apply such numerous and varied methods of case ascertainment, see Tables 1.1-1.3.

Though it was anticipated that the yield of unique cases from community methods of ascertainment would be low, it was conceivable that a small proportion of persons not fit for transfer to hospital would be missed by hospital based methods of ascertainment. Therefore, survey of G.P.s and nursing homes was incorporated into the methodology. Though the response rate from both nursing homes and general practice was relatively good, overall they contributed only 4% of cases to the study, and only 5 cases were not captured by other hospital based methods (unique-to-source cases). Therefore, future studies may consider that inclusion of community survey for case ascertainment may not be of significantly added value to justify the effort. The importance of using multiple methods of ascertainment is highlighted by the fact that no individual case was captured by all methods. Conversely none of the ascertainment sources captured >60% of the total cohort. The methodology employed during this study could be applied to other health care settings in whom reliable coded data is not available.

A novel method of assessment of under-ascertainment, not previously used in seizure or epilepsy incidence studies, was designed and implemented in this research. This involved prospective follow up of an 'at risk' patient cohort, namely those with primary or secondary brain tumours without a history of seizures, in order to identify first seizures and cross-reference them to the main database. As outlined in the 12 month data (section 3.4.3), a single case was identified using this method which was not captured using any of the other methods of ascertainment. This highlights the difficulty, perhaps impossibility, of identifying 100% of cases in an epidemiologic study and further highlights the need for multiple overlapping methods to reduce this risk in as much as is practically possible.

There are some potential limitations to the methodology implemented in this research thesis. The methodology used is significantly demanding in terms of time and manpower and may not be practically applicable in all other geographic areas. Alternatively, if an increased number of researchers are available, it may be possible to contact community settings more frequently and perhaps increase ascertainment rate from this source. In addition, though cases were captured

using prospective and retrospective methods, individual case demographic and clinical details were compiled from routinely collected clinical data. Therefore, clinical history and epilepsy specific risk factors were not consistently recorded in a standardized format. This limited interpretation of risk factors for seizures and epilepsy in an otherwise very well defined incidence cohort.

The General Data Protection Regulation (G.D.P.R.) came into force across the European Union on 25th May 2018. At the time of its enforcement, the data analysed for this thesis was anonymised. The need to obtain consent from all study participants in this particular study would have led to significant under-ascertainment as many patients were incapacitated for various reasons at the time of diagnosis of an incident seizure including death and severe illness. The application of G.D.P.R. to health research within Ireland remains a challenge for researchers. It may be difficult to design a study similar to that presented in this research thesis going forward, depending on the application of G.D.P.R. to national health research guidelines.

7.3 The incidence of first seizures, new diagnosis of epilepsy and seizure mimics; impact of the updated I.L.A.E. definition of epilepsy.

Application of the published methodological protocol[6] identified a total of 1942 medical records for review and, following exclusion of indeterminate and inappropriate cases, a total of 1264 cases were classified as first seizures, new diagnosis of epilepsy or a seizure mimic resulting in an annual incidence of 102, 62 and 94 per 100,000 population,[5, 7] respectively.

The most significant novel finding of this aspect of the research thesis is the finding that the incidence of new diagnosis of epilepsy was 54% higher when the updated 2014 I.L.A.E. definition of epilepsy[2] was applied compared to the 1993 definition.[8] To my knowledge, no other whole population epidemiologic study has reported results demonstrating the effect of the updated I.L.A.E. definition in adults. This finding is of relevance to epidemiologists, clinicians and those

involved in planning allocation of health resources. Potential reasons for the increased incidence may be that the 2014 definition may 'shift' the diagnosis of epilepsy to an earlier time-point, creating an early peak in a population whose incidence, if followed for a longer period, would ultimately be the same if the 1993 definition were applied. According to the 2014 definition, a follow up period of 10 years is needed to verify if such a shift has occurred, which may be practically difficult depending on the epidemiologic protocol used to ascertain cases. Alternatively, or concurrently, the 2014 definition may be less specific than the 1993 definition, allowing diagnosis of epilepsy in persons who will never go on to have a second seizure. This issue is complicated by commencement of an A.E.D. that, at least in the short-term, reduces the risk of a second seizure.

Consistent application of the updated 2014 I.L.A.E. definition across populations may be difficult as there is a lack of prospective studies on detailed and varied cohorts of patients to allow clinicians to accurately assess if an individual, following a single unprovoked seizure, is at approximately 60% or greater risk of recurrent seizures over the following ten years. Both for practicing neurologists and for future epidemiologic studies on the epidemiology of epilepsy, the results of this thesis highlight the potential difficulty that may occur when a clinical definition of a disease, which allows individual clinicians to infer diagnosis without strict criteria, is applied to an epidemiologic study. It is therefore important that the results of this research are replicated in different geographic areas.

This thesis presents the first incidence data on seizures and epilepsy available in Ireland and is therefore of significant value for health care planning and resource allocation at a national level. The characteristic bimodal age-specific incidence of seizures and epilepsy are similar to other studies and, when the 1993 definition is applied, the results are within the range of other similar geographic and social populations.

The occurrence of seizure mimics has been reported within some previous studies, though systematic ascertainment of their occurrence and annual incidence has not. Following application of a World Health Organization validated survey for detection of neurological disorders in a rural area in Tanzania, followed by assessment by a neurologist, Rwiza et al., 1992[9] reported a false positive prevalence of 15.5% based on the screening questionnaire. Recurrent febrile seizures were the most commonly encountered mimic. Similarly, Medina et al., 2005[10] reported a false positive prevalence of 8.8% following door-to-door survey followed by assessment by a neurologist in rural Honduras. Non-epileptic seizures, migraine and syncope were among the mimics detected. To our knowledge, no previous study has systematically captured seizure mimics within the same population as first seizures in order to better define this diverse group of disorders or presented incidence data on their occurrence. Our results demonstrate that this group of disorders represents a substantial workload to healthcare providers. Furthermore, the occurrence of mimics with potential significant morbidity and/or mortality, such as cardiogenic syncope and stroke, should be highlighted to frontline medical practitioners. A potential limitation of this study is that seizure mimics may be difficult to define from an epidemiologic perspective and variation in incidence of seizure mimics may occur if this study was repeated in different health settings.

7.4 Association between social deprivation and the incidence of first seizures, new diagnosis of epilepsy and seizure mimics.

The issue of socioeconomic deprivation as a risk factor for the development of epilepsy is important both at a regional and a global level. It has been established that the incidence of epilepsy is higher in developing countries compared to developed countries. This has been attributed to a higher incidence of certain risk factors for epilepsy, such as traumatic birth deficits and central nervous system infections. However, the influence of socioeconomic deprivation on epilepsy incidence within a country is less certain. One may speculate that social

drift, whereby a diagnosis of epilepsy puts an individual at risk of downward social drift, for example through loss of earning power, could increase the *prevalence* of epilepsy in lower socioeconomic groups. However, the results of this research thesis support other international studies demonstrating that relatively lower socioeconomic status is associated with the *development* of first-time seizures and epilepsy. Furthermore, the results of this research thesis are the first to report in detail that lower socioeconomic status is associated with the development of epilepsy of structural, genetic and unknown aetiologies of epilepsy. However, the number of cases within the genetic aetiology group were low and so these results must be interpreted with caution.

It is difficult to explain in a single theory the reasons why seizures and epilepsy are associated with relative socioeconomic deprivation. There may be a higher prevalence of neurodevelopemental disorders such as autism spectrum disorders in areas of relatively lower socioeconomic status.[11] Another potential, though unproven, explanation could be genetic clustering over many generations, whereby downward social drift of persons with genetic tendency to epilepsy, results in a higher prevalence of multiple, as yet not clearly defined, genetic polymorphisms which lower the threshold for seizure occurrence. Environmental stress and increased stress related hormones may lower seizure threshold, as has been shown in animal studies, which may be a factor in areas of socioeconomic deprivation.[12, 13] The results of this thesis suggest that multiple risk factors may be contributing and further study is needed to understand the aetiology of the association.

A potential limitation of this study is the use of area level markers, based on registered address, to determine the socioeconomic status of each case. Though similar methods to the Trutz Haase R.D.I. have been used in other studies investigating the association between socioeconomic status and the incidence of epilepsy,[14-17] such measures do not take into account individual level deprivation, whereby an individual may live in an area of relative socioeconomic deprivation, but are not themselves socially deprived. Furthermore, the Trutz Haase R.D.I. uses historically defined electoral divisions which are not evenly

defined in terms of either geographic area or population. This may increase misclassification of individual level deprivation. However, a prospective study, using systematically collected information on the socioeconomic status of individuals, would be difficult to perform at a population level. A second limitation, is the lack of prospectively collected data regarding individual risk factors for epilepsy, such as a family history of epilepsy or traumatic birth defects, which is necessary to further explore the mechanism of the association demonstrated in this study.

7.5 Causes and classification of all first unprovoked seizures and newly-diagnosed epilepsy in a defined geographic area

As outlined in section 7.2 above, application of multiple methods of case ascertainment followed by individual case analysis allowed for detailed reporting of the aetiology and classification of seizures and epilepsy in this research thesis. Similar to most, but not all, previously published incidence studies, this thesis reports a higher incidence of first unprovoked seizures and epilepsy among males compared to females and a higher incidence of focal onset seizures compared to generalized onset seizures. Structural aetiology was the most commonly determined cause and a relatively lower incidence of epilepsy of unknown aetiology compared to most previously reported studies is reported here. The results of this thesis highlights the importance of neuroimaging in assessment of new onset seizures and epilepsy to identify epilepsy associated structural brain abnormalities including new diagnosis of brain tumours. Many of the previous incidence studies did not incorporate M.R. imaging into the aetiological classification of seizures and epilepsy. Finally, this thesis explored the potential risk factors present amongst persons diagnosed with first unprovoked seizures compared to those diagnosed with a seizure mimic.

Detailed reporting of incident seizures and epilepsy, specifically with regard to aetiology, have been called for[18] and therefore the results of this thesis are of value to an international audience. This research thesis highlights the usefulness

of the updated I.L.A.E. classifications for seizures [3] and epilepsy [4] in a real world setting. However, this research thesis also highlights areas for potential clarification within those classification systems, such as the classification of epilepsy in persons with an underlying intellectual disability of unknown aetiology. No previous study has investigated the aetiology of epilepsy in Ireland and the results of this research thesis are of value to those planning health care services, specifically with regard to personnel skilled in diagnosis of epilepsy, interpretation of brain imaging and neurophysiological testing including E.E.G.

The main limitation of this aspect of the research thesis is the lack of prospectively collected individual case data regarding seizure and epilepsy related risk factors, which limited interpretation of this important issue. This area deserves further research at an international level in order to identify risk factors for the development of epilepsy and seizures.

7.6 The incidence and aetiology of acute symptomatic seizures in a defined geographic area

The incidence of acute symptomatic seizures is reported less frequently than that of unprovoked seizures or epilepsy and the results of this thesis are of value to the international community. Application of multiple overlapping methods of case ascertainment, including those methods specifically targeting persons who may be missed by routine screening of E.E.G. and radiology databases, resulted in an annual incidence of acute symptomatic seizures of 35 per 100,000 population.

The research presented in this thesis highlighted a potential gap in the I.L.A.E. guidelines for the definition of an acute symptomatic seizure.[19] Specifically, persons presenting with a seizure in the setting of systemic sepsis, are not clearly defined by the I.L.A.E. as acute symptomatic seizures. The I.L.A.E. acknowledges that there is a lack of systematic, published research as to what defines an acute symptomatic seizure. As demonstrated by the results of this thesis, a significant proportion of the cases of first acute symptomatic seizure

were not admitted to hospital primarily for seizures. Rather, the seizure occurred when they were admitted for another reason, reinforcing the validity of defining the case as acute symptomatic in nature.

The results of this study also highlight the significant burden on healthcare resources that alcohol and illicit drugs provide with regard to acute symptomatic seizures. Furthermore, a significant proportion of persons who had an acute symptomatic seizure during the study period, died during the hospital stay. This area deserves further study as to whether seizures are a marker of frailty, or rather whether the seizure contributed to the mortality rate.

The main limitation of the study of acute symptomatic seizures in this research thesis is the lack of prospectively and systematically collected data on risk factors which may help to predict persons particularly vulnerable to acute symptomatic seizures in the future.

7.7 Future directions

The 2011 I.L.A.E. standards for epidemiologic studies and epilepsy research[1] were published prior to the updated 2014 I.L.A.E. operational definition of epilepsy.[2] Though they acknowledge that epilepsy is defined by an enduring predisposition to epileptic seizures, they continue to encourage the 1993 I.L.A.E. definition[8] in epidemiologic research. Therefore, this research thesis presents incidence data using both the 1993[8] and 2014[2] definitions to allow comparison with previous studies. However, as the 2014 definition[2] is incorporated into routine clinical practise, the I.L.A.E. epidemiologic guidelines[1] may need to be updated to address this issue. Furthermore, future epidemiologic research using hospital based coded data is unlikely to be able to differentiate between cases meeting the 1993[8] and 2014[2] definitions. The data presented in this research thesis may aid future studies to estimate the proportion of cases meeting new and old criteria. Future detailed analysis of the aetiology of epilepsy and

longitudinal follow up of the 115 persons who met the 2014 definition[2] of epilepsy but did not qualify under the 1993 defintion[8] is planned.

As highlighted a number of times during discussion in this research thesis, further study is required in order to aid clinicians to estimate if an individual patient has an approximately 60% or greater risk of recurrent seizures over the following 10 years. This would require following a well-defined and heterogenous cohort of patients for up to 10 years. Detailed, systematically collected, data on risk factors for the occurrence of a first seizure and recurrent seizures would greatly enhance our understanding of the reasons for and risk of development of epilepsy in individuals.

The cohort of persons classified as seizure mimics in this research thesis and their specific diagnosis warrants further study. Just as seizures and epilepsy are subject to misdiagnosis, it may be that a number of cases diagnosed as seizure mimics, may in fact be converted to a diagnosis of epilepsy at some stage in the future. This highlights the fact that epilepsy is largely a clinical diagnosis, without a 'gold standard' biomarker in the vast majority of cases, and therefore carries with it a potential for misdiagnosis. Longer term follow up of this cohort of patients will be relevant to practising neurologists and clinicians.

The aetiology of the association between socioeconomic deprivation and incidence of epilepsy and seizures requires further study. As outlined above, improved understanding of the risk factors for development of seizures and epilepsy may aid researchers to develop methods to prevent development of epilepsy. Furthermore, this research highlights the need for increased resources for investigation and treatment of seizures and epilepsy in areas of relative socioeconomic deprivation.

Finally, the mortality associated with acute symptomatic seizures deserves further study. As outlined above, exploration of first acute symptomatic seizures as a marker of frailty and potential mortality could potentially be useful to

clinicians. Alternatively, exploration of whether the seizure itself contributed to the mortality of that case should also be explored.

7.8 Conclusions

Using detailed methodology adherent to international guidelines and definitions, this research thesis demonstrates novel protocols for investigations of first seizures and epilepsy within a defined population. It demonstrates a significantly increased incidence of epilepsy when updated international definitions are applied to a defined population. It is the first to report in detail the incidence and aetiology of seizures and epilepsy within Ireland, the first to provide incidence data on seizure mimics within any population and supports international evidence of an association between the incidence of seizures and epilepsy and socioeconomic deprivation. Finally, this research thesis provides a database for future study of the prognosis, mortality and remission rates for a detailed cohort of patients presenting with a first seizure, new diagnosis of epilepsy or a seizure mimic.

7.9 References

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Chapter 8 Presentations and Publications

8.1 Oral Presentations

1. 'Association between social deprivation and the incidence of first seizures, new diagnosis of epilepsy and seizure mimics'. American Academy of Neurology, Toronto, Canada, April 2020.

2. 'The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in a defined geographic area of Ireland'. Irish Neurological Association Meeting, Cork Ireland June 2019.
   Awarded Harold Millar Prize for best oral presentation.

3. 'Cork Epilepsy Incidence Study'. Registrar's Prize in Clinical Neuroscience, Dublin, November 2018.

4. 'Cork Epilepsy Incidence Study'. The Irish Chapter of the I.L.A.E., 8th Annual Expert Day, Dublin, September 2018

8.2 Article Publications

1. The incidence of first seizures, epilepsy and seizure mimics in a geographically defined area. EM Maloney, E Chaila, EJ O'Reilly, DJ Costello. Neurology 2020; Aug 4;95(5):e576-e590.

2. Application of recent international epidemiological guidelines to a prospective study of the incidence of first seizures, newly-diagnosed epilepsy and seizure mimics in a defined geographic region in Ireland. EM Maloney, E Chaila, EJ O'Reilly, DJ Costello. Neuroepidemiology 2019;53(3-4):225-236.

8.3 Abstract Publications

1. Association between social deprivation and the incidence of first seizures, new diagnosis of epilepsy and seizure mimics. EM Maloney, P Corcoran, DJ Costello, EJ O'Reilly. Neurology; 94 (15 Supplement) 2401.

2. The incidence of first seizures, new diagnosis of epilepsy, and seizure mimics in a defined geographic region of Ireland. E Maloney, E Chaila, E O'Reilly, D Costello. J Epidemiol Community Health 2019; 73 (Suppl 1):A1-A114

3. The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in County Cork, Ireland; an epidemiologic protocol. E Maloney, E O'Reilly, D Costello. Neurology 2018;90(15) Suppl P1.121

8.4 International Poster presentations

1. The incidence of first seizures, epilepsy and seizure mimics in a defined geographic area in 2017; implications of the 2014 ILAE operational definition of epilepsy EM Maloney, E Chaila, EJ O'Reilly, DJ Costello. American Epilepsy Society Meeting, Baltimore, December 2019.

2. The incidence of first seizures, epilepsy and seizure mimics in a geographically defined area in 2017. E Maloney, E Chaila, E O'Reilly, D Costello. I.L.A.E. British Branch Annual Scientific Meeting, Birmingham, October 2019.

3. The incidence of first seizures, new diagnosis of epilepsy, and seizure mimics in a defined geographic region of Ireland. E Maloney, E Chaila, E O'Reilly, D Costello. Joint European Congress of Epidemiology and Society of Social Medicine and Population Health Annual Scientific Meeting, Cork, September 2019.

4. The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in County Cork, Ireland; an epidemiologic protocol. E Maloney, E O'Reilly, D Costello. 31st International Congress of Clinical Neurophysiology, Washington, May 2018.

5. The incidence of first seizures, new diagnosis of epilepsy and seizure mimics in County Cork, Ireland; an epidemiologic protocol. E Maloney, E O'Reilly, D Costello. 70th American Academy of Neurology Annual Meeting, Los Angeles, April 2018.

Appendix 1

Neurology Journals

Standards of Reporting of Neurological Disorders (STROND): A Guideline for the reporting of incidence and prevalence studies in Neuroepidemiology Access article

Checklist

MS # _____

Section/Topic	Number	Recommendation	Manuscript page Number
TITLE & ABSTRACT			
Title and abstract	1	(a) Give the type of study design employed using a widely recognized term in the title or abstract.	
		(b) The abstract should give an accurate summary of how the study was conducted and the main findings.	
INTRODUCTION			
Background	2	Details of the scientific rationale for the study should be reported	
Aims and objectives	3	State the specific aims and objectives of the study.	
METHODS			
Study design	4	Give a full description of the study design	
	4a	*Give details of any study protocol (published or unpublished that gives additional useful information on the study design).*	
	4b	*If a pilot study has been conducted to inform the main study design then the findings should be referenced.*	
Setting	5	Clearly defined (usually, but not always, on a geographic basis), and stable, with reliable information on in- and out-migration.	
Source population	6	Description of how all eligible members of the population were identified and through what data sources (e.g. hospitals, outpatient clinics, death certificates).	
	6a	Source of data used for the study (e.g. administrative database, medical records). *If administrative database used algorithms for data extraction should be described.*	
	6b	*Description of the rate of hospital admission, (if applicable), for the neurological condition in the population.*	
	6c	*Details of health care system in the country (study region) where the study was conducted (e.g. public versus private health care system).*	
	6d	*Description of how a person with the neurological condition is referred (with the filters) in the country (study region) where the study was conducted.*	
	6e	Description and characteristics of response rate/drop outs and exclusion rate if applicable.	
Participants	7	Definition of cases is clearly identified and presented in sufficient detail.	
	7a	Details of the sampling method are described (are participants representative of the source population).	
	7b	Fully validated source of diagnosis or "reference-standard" criteria applied.	

	7c	Definition and justification of the disease severity (preferably using a standardized severity scale) or staging of the disease.	
	7d	Description of how types/subtypes of the neurological disorder of interest are distinguished (if relevant).	
	7e	Description of how completeness of case-ascertainment was assessed.	
	7f	*Description of whether completeness of case ascertainment was adequate.*	
Ethical approval	8	*Details of ethics approval / informed consent / data governance should be reported.*	
Measurement	9a	Incidence studies 1. Give details of how incidence was determined (based on timing of data collection either prospectively or retrospectively). 2. Definition and justification of timing of measurements. 3. The data presented to some specified time period (usually whole years or person-time). 4. Raw numbers are reported in sufficient detail to calculate the appropriate rates (e.g. by age or gender).	
	9b	Prevalence studies 1. Give details of specific time points over which estimates are derived (usually defined as the number of cases existing in a specific time point). 2. The data presented to some specified time period (usually whole years). 3. Raw numbers are reported in sufficient detail to calculate the appropriate rates (e.g. by age or gender).	
	9c	*If disease burden is to be assessed the study should report details of burden due to a variety of sources (e.g. disability, DALYs, symptoms, financial, caregiver etc…).*	
	9d	*Report any arrangements for quality checks / data verification / triangulation.*	
	9e	*Report details of the training of the person administering the instruments*	

Statistical methods	10	If rates have been standardised (e.g. by age or gender), then the details of the standard population used should be given.	
	10a	*If possible two standard populations should be used one with local relevance and the other to facilitate international comparisons.*	
	10b	Description of any assumptions made in the calculations should be reported.	
	10c	An explanation of how missing data was addressed in the analyses.	
	10d	*Provide a priori estimates of: sample size/power assessment/precision of estimates assessment.*	
	10e	Description of any sensitivity analyses.	
RESULTS			
Main findings	11	Consider a flow diagram that describes how participants were included in the study [useful in order to assess how a person with the neurological condition of interest is referred (with the filters)]	
	11a	Give appropriate rates with their associated 95% confidence intervals.	
	11b	Report results of any sensitivity analyses.	
DISCUSSION			
Key findings	12	Summarise the key findings in relation to the study aims and objectives.	
Limitations	13	Discuss potential limitations of the study.	
	13a	*Include details of risk of bias (e.g. selection bias), completeness of case ascertainment, and data quality (assessment of its probability, size and potential importance).*	
Interpretation	14	Interpret the results in the context of the evidence from other well performed studies with similar designs and objectives.	
	14a	Reliability of the estimates (i.e. based on the reporting of the statistical methodology, and study design, measurement of key information).	
Generalizability	15	Discuss the external validity of the study findings	
	15a	Are the results consistent with meta-analyses of descriptive epidemiological studies on the same topic that cover different settings (if applicable)?	

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University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

ECM 4 (dd) 15/11/16 & ECM 3 (hh) 06/12/16

1st December 2016

Dr Daniel Costello
Consultant Neurologist
Cork University Hospital
Wilton
Cork

Re: Incidence of new diagnosis of first seizures and epilepsy in Cork city and county over a one year period.

Dear Dr Costello

The Chairman approved the following:

- Cover Letter dated 14th November 2016
- Amendment Application form signed 14th November 2016
- Addition of Dr Eilis O'Reilly as a co-investigator in the above study
- Study Protocol Version 2 dated 14th November 2016
- Initial Letter to G.P.s Version 1 dated 14th November 2016
- Follow Up Letter to G.P.s Version 1 dated 14th November 2016
- Letter to other hospital consultants Version 1 dated 14th November 2016.

Full approval is now granted to begin the above study.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

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Ireland.

ECM 4 (dd) 15/11/16 & ECM 3 (ff) 07/02/17

20th January 2017

Dr Daniel Costello
Consultant Neurologist
Cork University Hospital
Wilton
Cork

Re: Incidence of new diagnosis of first seizures and epilepsy in Cork city and county over a one year period.

Dear Dr Costello

The Chairman approved the following:

- Amendment application form signed 3 January 2017
- Addition of Niamh Jones and Loretta Kennedy as co-investigators in the study
- Study protocol version 3 dated 3 January 2017
- Information leaflet version 1 dated 3 January 2017
- Consent form version 1 dated 3 January 2017.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

BON SECOURS HOSPITAL
Bon Secours Health System
College Road, Cork.
Tel: 021-4542807 Fax: 021-4542350

21st March 2017

Dr Daniel Costello
Department of Neurology
Cork University Hospital
Wilton
Cork

Dear Dr Costello

Study:

Incidence of new diagnosis of first seizures and epilepsy in Cork City and County over a one year period

The Management team of the Bon Secours Hospital, Cork has reviewed the application for the above study.

Approval has been granted by the Management team for the study to commence in the Hospital.

Yours sincerely

Harry Canning
Hospital Manager

Cork University Hospital
23 MAR 2017
Dept. of Neurology

cc. Ms Maeve Goggin, Quality Risk Manager, Bon Secours Hospital, College Road, Cork

Appendix 2

Incidence calculations for Chapter 5

All first unprovoked seizures

Age groups	ıles	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	6	163.18	3466	4	115.41	7143	10	140.00
1-4	15491	20	129.11	15008	7	46.64	30499	27	88.53
5-9	20625	16	77.58	19820	9	45.41	40445	25	61.81
10-14	18191	19	104.45	17253	8	46.37	35444	27	76.18
15-24	33952	19	55.96	33394	11	32.94	67346	30	44.55
25-34	35248	19	53.90	37596	9	23.94	72844	28	38.44
35-44	41970	14	33.36	42861	12	28.00	84831	26	30.65
45-54	36309	17	46.82	36000	13	36.11	72309	30	41.49
55-64	29092	21	72.18	29072	14	48.16	58164	35	60.17
65-74	21084	27	128.06	21732	23	105.83	42816	50	116.78
75-84	10440	29	277.78	12822	33	257.37	23262	62	266.53
>85	2596	7	269.65	5169	15	290.19	7765	22	283.32
Total	268675	214	79.65	274193	158	57.62	542868	372	68.52
		Male: female		1.382247433		Age-standardised			83.23

Single seizure <60% risk

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	1	27.20	3466	2	57.70	7143	3	42.00
1-4	15491	5	32.28	15008	2	13.33	30499	7	22.95
5-9	20625	2	9.70	19820	2	10.09	40445	4	9.89
10-14	18191	4	21.99	17253	1	5.80	35444	5	14.11
15-24	33952	9	26.51	33394	2	5.99	67346	11	16.33
25-34	35248	6	17.02	37596	1	2.66	72844	7	9.61
35-44	41970	3	7.15	42861	5	11.67	84831	8	9.43
45-54	36309	2	5.51	36000	2	5.56	72309	4	5.53
55-64	29092	2	6.87	29072	1	3.44	58164	3	5.16
65-74	21084	4	18.97	21732	3	13.80	42816	7	16.35
75-84	10440	3	28.74	12822	3	23.40	23262	6	25.79
>85	2596	1	38.52	5169	1	19.35	7765	2	25.76
Total	268675	42	15.63	274193	25	9.12	542868	67	12.34
		Male:female		1.714503545		Age-standardised			14.42

Single seizure >60% risk

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	1	27.20	3466	0	0.00	7143	1	14.00
1-4	15491	6	38.73	15008	1	6.66	30499	7	22.95
5-9	20625	1	4.85	19820	1	5.05	40445	2	4.94
10-14	18191	6	32.98	17253	1	5.80	35444	7	19.75
15-24	33952	2	5.89	33394	1	2.99	67346	3	4.45
25-34	35248	6	17.02	37596	2	5.32	72844	8	10.98
35-44	41970	3	7.15	42861	3	7.00	84831	6	7.07
45-54	36309	9	24.79	36000	6	16.67	72309	15	20.74
55-64	29092	11	37.81	29072	7	24.08	58164	18	30.95
65-74	21084	9	42.69	21732	6	27.61	42816	15	35.03
75-84	10440	12	114.94	12822	11	85.79	23262	23	98.87
>85	2596	2	77.04	5169	8	154.77	7765	10	128.78
Total	268675	68	25.31	274193	47	17.14	542868	115	21.18
			Male:female	1.47652281		Age-standardised			26.18

Multiple seizures

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	4	108.78	3466	2	57.70	7143	6	84.00
1-4	15491	10	64.55	15008	5	33.32	30499	15	49.18
5-9	20625	15	72.73	19820	8	40.36	40445	23	56.87
10-14	18191	10	54.97	17253	7	40.57	35444	17	47.96
15-24	33952	14	41.23	33394	11	32.94	67346	25	37.12
25-34	35248	10	28.37	37596	7	18.62	72844	17	23.34
35-44	41970	10	23.83	42861	4	9.33	84831	14	16.50
45-54	36309	7	19.28	36000	6	16.67	72309	13	17.98
55-64	29092	9	30.94	29072	6	20.64	58164	15	25.79
65-74	21084	16	75.89	21732	16	73.62	42816	32	74.74
75-84	10440	14	134.10	12822	20	155.98	23262	34	146.16
>85	2596	4	154.08	5169	6	116.08	7765	10	128.78
Total	268675	123	45.78	274193	98	35.74	542868	221	40.71
	Male:Female ratio		1.34			Age-standardised			74.41

New diagnosis of epilepsy

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	5	135.98	3466	2	57.70	7143	7	98.00
1-4	15491	16	103.29	15008	6	39.98	30499	22	72.13
5-9	20625	16	77.58	19820	9	45.41	40445	25	61.81
10-14	18191	16	87.96	17253	8	46.37	35444	24	67.71
15-24	33952	16	47.13	33394	12	35.93	67346	28	41.58
25-34	35248	16	45.39	37596	9	23.94	72844	25	34.32
35-44	41970	13	30.97	42861	7	16.33	84831	20	23.58
45-54	36309	16	44.07	36000	12	33.33	72309	28	38.72
55-64	29092	20	68.75	29072	13	44.72	58164	33	56.74
65-74	21084	25	118.57	21732	22	101.23	42816	47	109.77
75-84	10440	26	249.04	12822	31	241.77	23262	57	245.03
>85	2596	6	231.12	5169	14	270.85	7765	20	257.57
Total	268675	191	71.09	274193	145	52.88	542868	336	61.89

All first unprovoked seizures

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	6	163.18	3466	4	115.41	7143	10	140.00
1-4	15491	20	129.11	15008	7	46.64	30499	27	88.53
5-9	20625	16	77.58	19820	9	45.41	40445	25	61.81
10-14	18191	19	104.45	17253	8	46.37	35444	27	76.18
15-24	33952	19	55.96	33394	11	32.94	67346	30	44.55
25-34	35248	19	53.90	37596	9	23.94	72844	28	38.44
35-44	41970	14	33.36	42861	12	28.00	84831	26	30.65
45-54	36309	17	46.82	36000	13	36.11	72309	30	41.49
55-64	29092	21	72.18	29072	14	48.16	58164	35	60.17
Total	234555	151	64.38	234470	87	37.10	469025	238	50.74
65-74	21084	27	128.06	21732	23	105.83	42816	50	116.78
75-84	10440	29	277.78	12822	33	257.37	23262	62	266.53
>85	2596	7	269.65	5169	15	290.19	7765	22	283.32
Total	34120	63	184.64	39723	71	178.74	73843	134	181.47

Single seizure <60% risk

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	1	27.20	3466	2	57.70	7143	3	42.00
1-4	15491	5	32.28	15008	2	13.33	30499	7	22.95
5-9	20625	2	9.70	19820	2	10.09	40445	4	9.89
10-14	18191	4	21.99	17253	1	5.80	35444	5	14.11
15-24	33952	9	26.51	33394	2	5.99	67346	11	16.33
25-34	35248	6	17.02	37596	1	2.66	72844	7	9.61
35-44	41970	3	7.15	42861	5	11.67	84831	8	9.43
45-54	36309	2	5.51	36000	2	5.56	72309	4	5.53
55-64	29092	2	6.87	29072	1	3.44	58164	3	5.16
Total	234555	34	14.50	234470	18	7.68	469025	52	11.09
65-74	21084	4	18.97	21732	3	13.80	42816	7	16.35
75-84	10440	3	28.74	12822	3	23.40	23262	6	25.79
>85	2596	1	38.52	5169	1	19.35	7765	2	25.76
Total	34120	8	23.45	39723	7	17.62	73843	15	20.31

New diagnosis of epilepsy

Age groups	Males	Cases	Incidence	Females	Cases	Incidence	Total	Cases	Incidence
<1	3677	5	135.98	3466	2	57.70	7143	7	98.00
1-4	15491	16	103.29	15008	6	39.98	30499	22	72.13
5-9	20625	16	77.58	19820	9	45.41	40445	25	61.81
10-14	18191	16	87.96	17253	8	46.37	35444	24	67.71
15-24	33952	16	47.13	33394	12	35.93	67346	28	41.58
25-34	35248	16	45.39	37596	9	23.94	72844	25	34.32
35-44	41970	13	30.97	42861	7	16.33	84831	20	23.58
45-54	36309	16	44.07	36000	12	33.33	72309	28	38.72
55-64	29092	20	68.75	29072	13	44.72	58164	33	56.74
Total	234555	134	57.13	234470	78	33.27	469025	212	45.20
65-74	21084	25	118.57	21732	22	101.23	42816	47	109.77
75-84	10440	26	249.04	12822	31	241.77	23262	57	245.03
>85	2596	6	231.12	5169	14	270.85	7765	20	257.57
Total	34120	57	167.06	39723	67	168.67	73843	124	167.92

Incidence calculations for chapter 6

First acute symptomatic seizures (all aetiology)

Age groups	Males	Number	Incidence	Females	Number	Incidence	Total Population	Number	Incidence
<1	3677	1	27.20	3466	1	28.85	7143	2	28.00
1-4	15491	3	19.37	15008	1	6.66	30499	4	13.12
5-9	20625	3	14.55	19820	1	5.05	40445	4	9.89
10-14	18191	0	0.00	17253	0	0.00	35444	0	0.00
15-24	33952	9	26.51	33394	4	11.98	67346	13	19.30
25-34	35248	23	65.25	37596	7	18.62	72844	30	41.18
35-44	41970	15	35.74	42861	5	11.67	84831	20	23.58
45-54	36309	11	30.30	36000	4	11.11	72309	15	20.74
55-64	29092	21	72.18	29072	15	51.60	58164	36	61.89
65-74	21084	13	61.66	21732	11	50.62	42816	24	56.05
75-84	10440	23	220.31	12822	7	54.59	23262	30	128.97
>85	2596	2	77.04	5169	9	174.11	7765	11	141.66
Total	268675	124	46.15	274193	65	23.71	542868	189	34.82

Male: female Rate ratio	1.95	Age-standardised incidence	41.72

First acute symptomatic seizures not excluding those due to sepsis

Age groups	Males	Number	Incidence	Females	Number	Incidence	Total Population	Number	Incidence
<1	3677	0	0.00	3466	1	28.85	7143	1	14.00
1-4	15491	3	19.37	15008	1	6.66	30499	4	13.12
5-9	20625	3	14.55	19820	1	5.05	40445	4	9.89
10-14	18191	0	0.00	17253	0	0.00	35444	0	0.00
15-24	33952	9	26.51	33394	4	11.98	67346	13	19.30
25-34	35248	23	65.25	37596	7	18.62	72844	30	41.18
35-44	41970	15	35.74	42861	5	11.67	84831	20	23.58
45-54	36309	10	27.54	36000	4	11.11	72309	14	19.36
55-64	29092	20	68.75	29072	14	48.16	58164	34	58.46
65-74	21084	9	42.69	21732	9	41.41	42816	18	42.04
75-84	10440	17	162.84	12822	5	39.00	23262	22	94.57
>85	2596	1	38.52	5169	5	96.73	7765	6	77.27
Total	268675	110	40.94	274193	56	20.42	542868	166	30.58

Male: female Rate ratio	2.00	Age-standardised incidence	35.00

First acute symptomatic seizures due alcohol and/or illicit drugs only

Age groups	Males	Number	Incidence	Females	Number	Incidence	Total population	Number	Incidence
<1	3677	0	0.00	3466	0	0.00	7143	0	0.00
1-4	15491	0	0.00	15008	0	0.00	30499	0	0.00
5-9	20625	0	0.00	19820	0	0.00	40445	0	0.00
10-14	18191	0	0.00	17253	0	0.00	35444	0	0.00
15-24	33952	9	26.51	33394	1	2.99	67346	10	14.85
25-34	35248	17	48.23	37596	2	5.32	72844	19	26.08
35-44	41970	11	26.21	42861	3	7.00	84831	14	16.50
45-54	36309	7	19.28	36000	0	0.00	72309	7	9.68
55-64	29092	15	51.56	29072	9	30.96	58164	24	41.26
65-74	21084	3	14.23	21732	3	13.80	42816	6	14.01
75-84	10440	2	19.16	12822	1	7.80	23262	3	12.90
>85	2596	0	0.00	5169	1	19.35	7765	1	12.88
Total	268675	64	23.82	274193	20	7.29	542868	84	15.47
Male: female Rate ratio			3.27			Age-standardised incidence			16.42

First acute symptomatic seizures due to all aetiology except alcohol and/or illicit drug abuse

Age groups	Males	Number	Incidence	Females	Number	Incidence	Total population	Number	Incidence
<1	3677	1	27.20	3466	1	28.85	7143	2	28.00
1-4	15491	3	19.37	15008	1	6.66	30499	4	13.12
5-9	20625	3	14.55	19820	1	5.05	40445	4	9.89
10-14	18191	0	0.00	17253	0	0.00	35444	0	0.00
15-24	33952	0	0.00	33394	3	8.98	67346	3	4.45
25-34	35248	6	17.02	37596	5	13.30	72844	11	15.10
35-44	41970	4	9.53	42861	2	4.67	84831	6	7.07
45-54	36309	4	11.02	36000	4	11.11	72309	8	11.06
55-64	29092	6	20.62	29072	6	20.64	58164	12	20.63
65-74	21084	10	47.43	21732	8	36.81	42816	18	42.04
75-84	10440	21	201.15	12822	6	46.79	23262	27	116.07
>85	2596	2	77.04	5169	8	154.77	7765	10	128.78
Total	268675	60	22.33	274193	45	16.41	542868	105	19.34
Male: female Rate ratio			1.36			Age-standardised incidence			25.29