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The incidence of first seizures, epilepsy and seizure mimics in a geographically defined area

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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 (ILAE) 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 geographical 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 ILAE definitions.
Results: When applying the 2014 ILAE 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 ILAE 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.

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1. 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 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 (ILAE) 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 ILAE 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[6] 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.

2. Methods

2.1 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 STROND guidelines.[9]

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2.2 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 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 ILAE 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 ILAE operational definitions.[6, 11] Epilepsy type was classified as focal, generalised or unknown according to the 2017 ILAE 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 ILAE 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 (GP)), 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

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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 ILAE 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 (EEG)[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 (DC and EC) on how likely was a patient to have further seizure(s) over the next 10 years if not started on an anti-epileptic drug (AED). 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 AED. 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.

2.3 Statistical analysis

Demographic data are presented as median and interquartile range. 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.

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2.4 Standard Protocol Approvals, Registrations, and Patient Consents

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

2.5 Data Availability

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

3. Results

3.1 Case capture and inclusion

Figure 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 EEG 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 EEG databases provided the largest number of included cases (n=748, 56%) and the largest number of unique-to-source cases (n=302, 23%).

3.2 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 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 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

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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 ILAE definition[5] (i.e. a history of two or more unprovoked seizures), see Table 2. Similar to the 2014 ILAE definition,[6] incidence displayed a bimodal age distribution, see Figure 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 AED. Ninety-three percent (n=206) of those with a definite or probable diagnosis of epilepsy according to the 1993 definition[5] were prescribed an AED.

The incidence of seizure mimics was almost equal to the incidence of first seizures, see Figure 4 and Table 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 (interquartile range 9) for all first seizures (n=722) and 4 days (interquartile range 7) for all seizure mimics (n=510).

3.3. 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 AED. The patient did not have an EEG or dedicated brain imaging.

4. Discussion

We sought to estimate incidence of first seizures, new diagnosis of epilepsy, and seizure mimics in a defined geographical area adhering to ILAE guidelines. The ILAE 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

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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 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 AED 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 ILAE definition changed during the Norwegian study period. It is possible that children were commenced on an AED 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 AED. Our data demonstrated that over 90% of patients were prescribed an AED 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,

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for example if a patient has a remote history of a cortical infarct.[18] The Multicentre Trial for Early Epilepsy and Single Seizures (MESS)[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 AED. 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 AED 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 (RASC) of whom 13% (n=9) had been commenced on an AED 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 AED medication and, in some cases, may detect potentially dangerous conditions such as cardiogenic syncope.

The ILAE 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

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individual case analysis in a previously unstudied geographic area and reporting of results in accordance with updated ILAE 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 EEG 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 compares the current study to previously published whole population data in terms of case ascertainment methodology and incidence results. When using the 1993 ILAE 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 RASC operates a 3-4 week waiting list for new referrals and is readily accessible to GPs. The majority of GPs would not commence or titrate AEDs 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 GP, thus prompting community survey as part of our case ascertainment. Four percent (n=51) of cases were ascertained by either GP 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 GPs 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 GPs agreed to actively participate in order to identify all incident neurological

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diagnosis. It would not have been practical within the geographical area included in our study, which included over 350 GPs 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 (HIPE) data in Ireland is not designed for research and the validity of HIPE data with regard to epilepsy is unknown. Furthermore, seizures occurring in medically unwell patients admitted for other reasons may not be coded. HIPE data does not differentiate between new onset seizures and admission for established epilepsy. Finally, HIPE 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, HIPE 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 ILAE 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.

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Appendix 1: Authors

Name	Location	Contribution
Eimer Maloney, MD	University College Cork	Literature search; study concept and design; data collection analysis and interpretation; manuscript composition.
Elijah Chaila, MD	University Hospital Limerick	data collection and interpretation; manuscript editing.
Éilis O'Reilly, ScD	University College Cork	study concept and design; data analysis and interpretation; manuscript editing.
Daniel Costello, MD	University Hospital Cork	study concept and design; data collection; analysis and interpretation; manuscript editing

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Figure titles and legends

Figure 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 ILAE epidemiologic guidelines.[4] Cases in whom an alternate diagnosis was reached were classified as seizure mimics. *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 2. Unadjusted annual incidence rates.

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. The annual incidence of epilepsy according to the 1993[5] and 2014[6] ILAE definitions.

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

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Figure 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.

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Tables

Table 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 geographical area for the calendar year 2017. M:F Ratio= male to female incidence ratio.

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 geographica area for the calendar year 2017.

Annual incidence of all first sezirues

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)**			**94-11**
	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

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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

Annual incidence of new diagnosis of epilepsy according to the 2014 ILAE 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**

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Male:female incidence ratio	0.89	Age standardised incidence		111

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Table 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 ILAE definition of epilepsy.[5] M:F Ratio= male to female incidence ratio.

The sex-specific, age-group specific and total crude and age- standardised incidence of definite and probable new diagnosis made according to the 1993 ILAE 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

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Table 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. AED =Anti-epileptic drug. EEG= electroencephalogram. RASC= Rapid Access Seizure Clinic. GP= General practitioner.

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																				
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 ILAE 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 ILAE 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 ILAE definition	**74 age adjusted to Europe**																			

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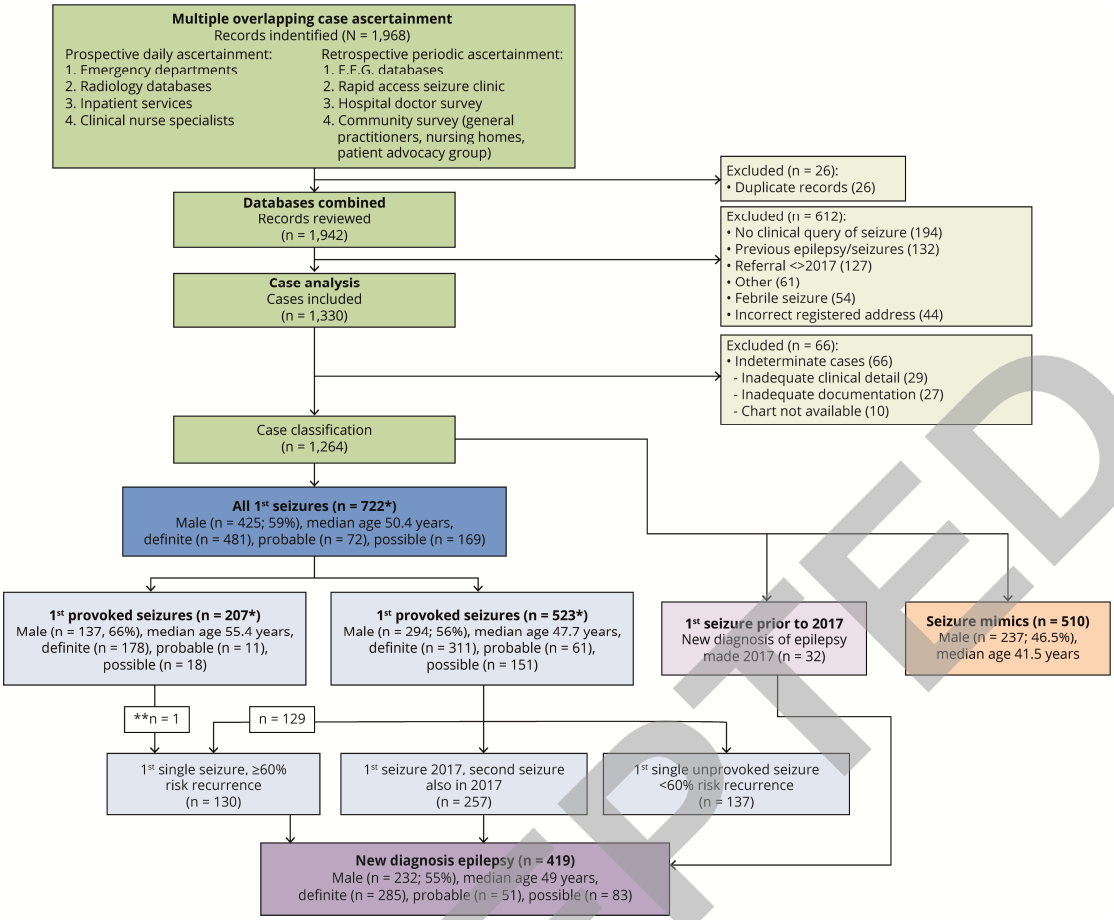
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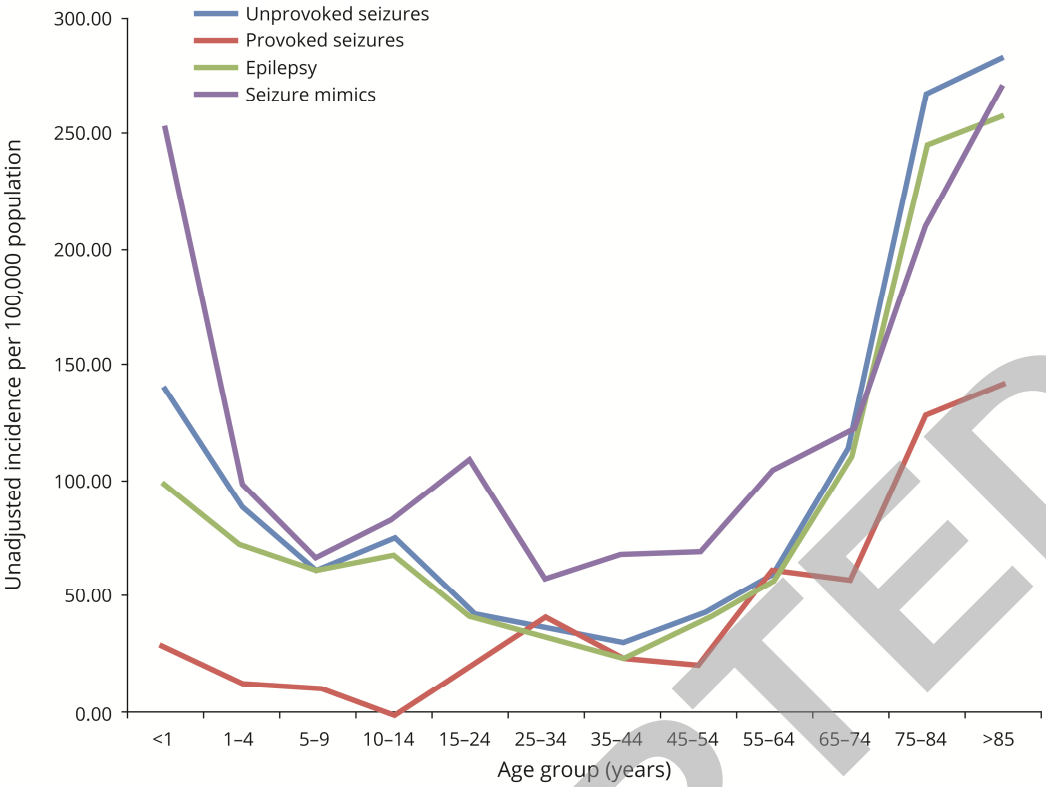
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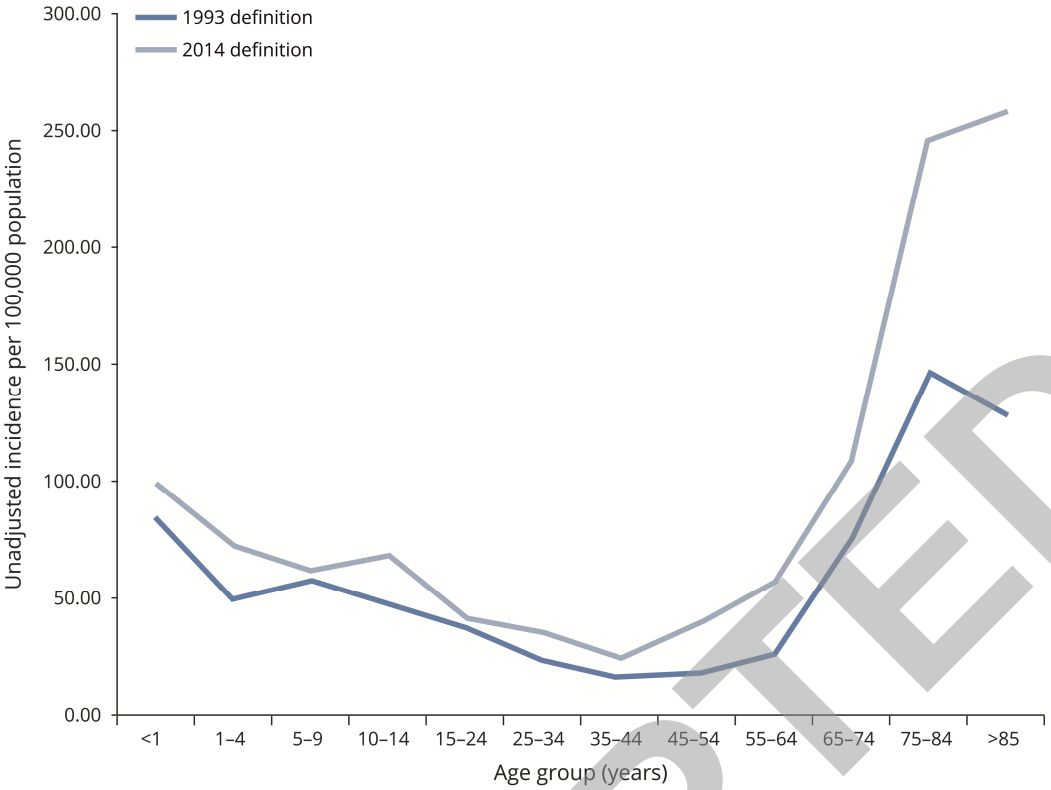
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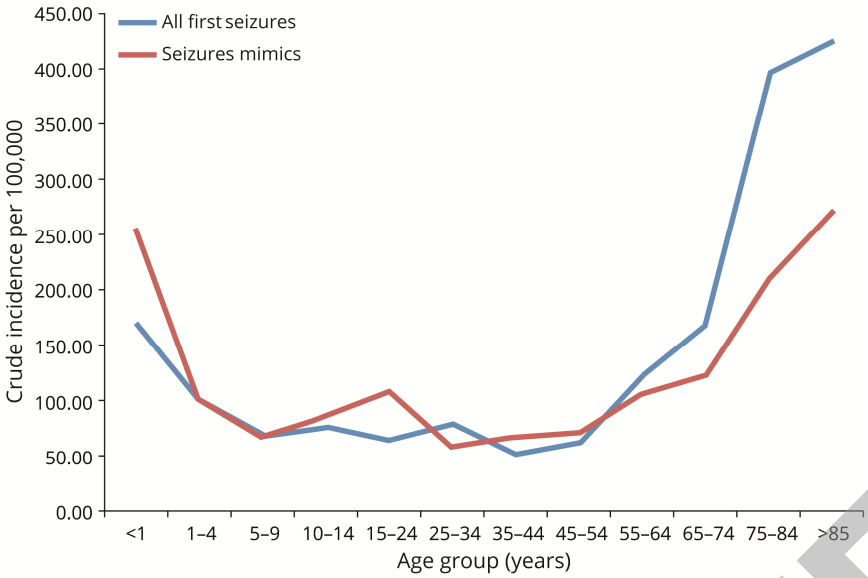
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