The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy

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Summary

Objectives: Since previous reviews of epidemiologic studies of premature mortality among people with epilepsy were completed several years ago, a large body of new evidence about this subject has been published. We aim to update prior reviews of mortality in epilepsy and to re-evaluate and quantify the risks, potential risk factors, and causes of these deaths.

Methods: We systematically searched the MEDLINE and EMBASE databases to identify published reports describing mortality risks in cohorts and populations of people with epilepsy. We reviewed relevant reports and applied criteria to identify those studies likely to accurately quantify these risks in representative populations. From these we extracted and summarized the reported data.

Results: All population-based studies reported an increased risk of premature mortality among people with epilepsy compared to general populations. Standard mortality ratios are especially high among people with epilepsy aged less than 50 years, among those whose epilepsy is categorized as structural/metabolic, those whose seizures do not fully remit under treatment, and those with convulsive seizures. Among deaths directly attributable to epilepsy or seizures, important immediate causes include sudden unexpected death in epilepsy, status epilepticus, unintentional injuries, and suicide.

Significance: Epilepsy-associated premature mortality imposes a significant public health burden, and many of the specific causes of death are potentially preventable. These require increased attention from health care providers, researchers, and public health professionals.

Keywords: Seizures, convulsions, death, developed countries, resource-rich countries, premature mortality

Key Points:

- Epilepsy-associated mortality imposes a significant burden on the public health of high-income countries
- Important causes of death among people with epilepsy include injuries, status epilepticus, and SUDEP, which may be preventable with access to high quality specialty health care.
- Limitations of existing studies of epilepsy-associated mortality indicate a need for additional epidemiologic studies and the development of methods and systems for long-term surveillance of mortality in people with epilepsy.

Introduction

Previous reviews focused on epidemiologic studies of all-cause mortality among people with epilepsy[1-5] have found that the condition carries an overall increased risk of premature death, have identified risk factors and characteristics of epilepsy associated with premature mortality, and have provided information on the proportions of deaths attributable to specific causes among people with epilepsy. These reviews also reveal considerable variability in these estimates.

The variability in such estimates can be mainly attributed to actual differences in risk of premature death among the various populations ascertained and to differences in study methodology. Valid methods for determining death in people with epilepsy depend on accurate diagnoses of epilepsy, as well as complete and accurate determinations of the numbers of deaths and the specific causes thereof among the populations studied. If studies are population-based, full ascertainment of epilepsy cases in those populations is necessary. Most reviews to date have not systematically characterized the quality of methods among the published reviews.

The reviews cited above were completed several years ago and since then a large body of new evidence about mortality in epilepsy has been published. Accordingly, there is a need to assess systematically new and older evidence, specifically for high-income world regions as well as low- and middle-income world regions. This evidence is essential for assigning priorities for prevention strategies.

This review aims to update past assessments of the epidemiology of premature mortality among people with epilepsy. We also aim to re-evaluate and quantify risks, risk factors, and causes of these deaths, with special attention to deaths consequent to the underlying etiologies of epilepsy and deaths consequent to epilepsy itself or its treatment. Where this review identifies preventable causes, this knowledge will support the development of strategies and programs to reduce the burden of mortality in epilepsy. This review focuses on mortality in high~~er~~-income countries (HIC); a companion review focuses on mortality in lower- and middle-income countries.

Methods

In this systematic review we used standards provided in "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement."[6]

Definitions. Various measures of risk are employed among published studies of mortality in epilepsy, which sometimes impose difficulties comparing findings across studies. In this review we consider both absolute and comparative risk measures.

Incidence rates of death or specific causes of death are absolute measures that may be reported in population-based studies. We describe incidence rates as annual numbers of deaths per 1000 persons with epilepsy.

Many studies also employ comparative risk measures, intended to convey the relative magnitude of risk among population groups. Within subpopulations of a study,

incidence rates may be compared using a rate ratio (RR), which may be crude or adjusted for potentially confounding variables such as age and sex. Incidence rates between studies are best compared when they are directly standardized by age (or age and sex) to the same reference population. A similar comparative incidence measure is the hazard ratio (HR), which takes more detailed account of individual subject survival time, using regression modelling.[7]

The standardized mortality ratio (SMR) is the ~~commonest~~ most common comparative risk measure encountered in this review. This is defined as the ratio of the observed numbers of deaths in the study population (with epilepsy) to the expected number of deaths estimated by standardization to the reference population (without epilepsy). The reference population is usually the base population of the study. Thus, SMRs are standardized only within each study, and because distributions of subject characteristics such as age, sex, and other extraneous mortality risk factors may vary considerably among different studies, comparisons of SMRs between studies must be made with caution because of the likelihood of residual confounding by such factors.[7]

Other comparative risk measures occasionally encountered in this review are odds ratios (ORs) employed in case-control studies and multivariate analyses.

Search strategy. We used the Ovid® MEDLINE ~~(Ovid)~~ and Embase® database search engines to find relevant references. Search terms in MEDLINE included any of the following Medical Subject Headings, with subheadings indicated by brackets and term combinations indicated by 'AND' used as a Boolean operator:

- Epilepsy [epidemiology] AND Epilepsy [mortality]
- Epilepsy AND Mortality
- Epilepsy AND 'Sudden death' [epidemiology]
- Epilepsy AND Death [etiology]
- Epilepsy AND 'Wounds and Injuries' (and subheadings) [mortality]

We did not restrict the search by language, but limited our search to human studies and excluded case reports. Similarly, we also used the EMBASE search engine to retrieve references indexed under both epilepsy and mortality, when both subjects were indicated as the focus of the report. We reviewed the retrieved titles and abstracts to identify original reports that provided new data including measures of mortality for people with epilepsy, e.g., mortality incidence rates, SMRs, proportionate mortality ratios, or other comparative risk ratios. We included studies that were population- or community-based, as well as clinical cohort or case-control studies. We obtained and reviewed full-length reports for all references whose titles or abstracts suggested the articles might meet these criteria. The full search strategy using both database search engines—and the criteria for screening titles and abstracts—are described in Supporting Table 1a.

Evaluation of strength of evidence. These full reports were each examined by a pair of reviewers, who assessed their relevancy, strength of evidence, and who abstracted relevant data. Differences in assessments of relevance or quality of evidence were resolved by consensus of the reviewer pairs after reconsideration. The criteria by which we assessed the quality of evidence included:

- sensitivity of epilepsy case ascertainment,
- sensitivity of mortality case ascertainment,
- accuracy of diagnoses of epilepsy,
- accuracy of diagnoses of cause of death,
- representativeness of the study population.

We assigned each report to categories designated as Class 1 through Class 4, representing ~~highest~~ strongest through ~~lowest~~ weakest strength of evidence, respectively. From the bibliographic citations of Class 1 – 3 articles, we also sought relevant eligible reports not previously identified in the original search and screening efforts. A more complete description of these quality assessment criteria and corresponding classes of evidence is included in Supporting Table 1b available online.

Findings

Search results. Searches of MEDLINE and E~~MBASE~~mbase conducted in November 2011 and updated in February 2014 and June 2016 in sum yielded ~~495~~ 607 article citations. Results of the search and screening are detailed in Figure 1. A total of ~~54~~ 46 reports met all inclusion criteria with strength of evidence rated ≥ 'Class 3', representing high-income countries. Although three reports represented different findings over time from a single cohort from the United Kingdom[8-10] and two reports from a single cohort in Austria[11; 12], their findings were included when they represented separate measurements.

Overall risk of mortality. Seventeen studies provided SMRs estimating the risk of premature death for people with epilepsy compared to reference populations as shown in Table 1. Nine of these were population-based, including all ages or all adult ages,[8; 10; 13-19] two of which represented the same cohort.[8; 10] All of these nine showed significant elevations of their SMRs ranging from 1.6 to 3.0. Among 6 of these population-based studies representing incidence cohorts including all ages, the weighted median SMR was 2.3. Among three population-based studies of children[20-22] there were considerably higher SMRs ranging from 6.4 to 7.5.

~~Three~~ Four clinic- or hospital-based cohort studies of epilepsy patients, including all ages or all adults, yielded SMRs ranging from 1.4 to 3.6.[11; 12; 23; 24] Two clinic-based cohort studies of children yielded higher SMRs of 7.0 and 7.5.[25; 26]

Mortality risk by sex. Supporting Table 2 summarizes the findings of seven studies comparing risks of death from all causes between females and males.[12-14; 16; 17; 24; 27] With one exception,[27] studies showed elevated SMRs for both females and males.

Mortality risk by age. Nine studies reported age-specific SMRs for people with epilepsy. summarized in Supporting Table 3. [8; 14; 16; 20; 22; 24-26; 28] The highest SMR (22.3) represented persons with onset of epilepsy in the first year of life. Considering only class 1 and 2 studies that report SMRs by age-at-death interval,[8; 14; 20; 22] consistently higher SMRs were reported in all age groups younger than 45 years (range 6.4 to 8.5), while comparatively lower SMR elevations were reported in age groups older than 64 years (range 1.4 to 2.6). The distribution of SMRs by age at death is illustrated in Figure 2.

Risk by interval from time of diagnosis. Class 1 and 2 incident cohort studies of three populations of people diagnosed with epilepsy or unprovoked seizures reported higher SMRs during the earliest measured time intervals following diagnosis, diminishing in subsequent intervals (Figure 3).[14; 15; 18] This effect may, however, in part be attributable to confounding by age, considering that epilepsy incidence is higher in children for whom mortality rates of the base population are lower than among older populations. We also found that among Class 2 studies that measured mortality separately for remote symptomatic epilepsy vs. idiopathic or cryptogenic epilepsy, the early elevation of mortality risk after diagnosis was mainly observed in the symptomatic group.[18; 29]

Risk by seizure type. Three population-based cohort studies of incident epilepsy[16; 19] or incident epilepsy and first unprovoked seizure[13] provided estimates of risk according to the type of seizures experienced by their subjects as listed in Supporting Table 4. For those with generalized tonic-clonic seizures, a Swedish study[16] reported a significantly elevated SMR of 3.9 for males; the corresponding SMR was also elevated for females, but not at a statistically significant level. For subjects with partial seizures with secondary generalization, an Estonian study[19] reported an SMR of 2.7, compared to an SMR of 1.5 for subjects with simple partial seizures. For those with focal seizures not further characterized, two studies[13; 16] reported significantly elevated SMRs of 2.1 and 1.8. One of these reported only a slight, statistically insignificant elevation of SMR of 1.3 among those in their cohort with generalized seizures that were not further classified.[13]

Risk by etiology of epilepsy. Nine studies[8; 10; 12-15; 18; 19; 23] summarized in Supporting Table 5 reported SMRs according to these broad categories of cause of epilepsy: cryptogenic, idiopathic, or symptomatic.[*] The highest risks are measured among people with epilepsy with symptomatic seizures; among class 1 and 2 studies, [8; 10; 13-15; 18; 19] SMRs were all significantly elevated, with a range of 2.2 to 4.3. Modest SMR elevations were observed in most class 1 and 2 studies addressing cryptogenic or idiopathic causes, [8; 10; 13-15; 18; 19] with estimates ranging from 0.9 to 2.1, only some of which were statistically significant.

Risk by comorbid brain disorders among people with epilepsy. Table 2 describes data from ~~eleven~~ thirteen studies that assessed the risk of death among subjects with comorbid neurologic conditions ~~considered to be~~potentially causal to their epilepsy.[8-11; 14; 15; 20; 21; 25; 26; 30-32] Very high measurements of risk, with SMRs ranging from 11 to 50, were found for subjects with central nervous system conditions described in various general terms among the studies, summarized here as static or progressive encephalopathies, including major congenital and acquired central nervous system deficits. Similarly high measurements of risk were also found for the more specific category comprising intellectual disability (mental retardation) and cerebral palsy, and for the category of brain tumor. Lesser, but still substantial risk elevations were found in people with epilepsy attributed to cerebrovascular disease or to diseases characterized by dementia.

[*] These categories are described in terminologies of older International League Against Epilepsy (ILAE) classifications that were in effect at the times these studies were completed. These older descriptors of etiology correspond approximately to newer terms recommended in 2010 by the ILAE Commission on Classification and Terminology as follows: 'cryptogenic' – unknown, 'idiopathic' – genetic or presumed genetic, and 'symptomatic' – structural-metabolic.

Risk in people still having seizures under treatment. Seven cohort studies summarized in Supporting Table 6 estimated risk of death among various epilepsy populations known or likely to have continued seizures despite treatment.[12; 33-38] All measures indicated elevated levels of risk. Rate ratios (RRs) comparing risk to people with epilepsy who are seizure-free were especially high, with estimates of 9.3 and 13.4.[34; 35]

Risk of sudden unexpected death in epilepsy (SUDEP). The risk of SUDEP, which excludes deaths attributable to structural or external causes determined from death investigation or prior clinical diagnosis, is estimated in two groups of studies: general community-based populations and clinical cohorts. As summarized in Supporting Table 7, SUDEP occurrence in general populations of people with epilepsy was addressed by 8 community-based studies,[23; 39-44] among which reported rates varied substantially. Among studies including all age groups,[23; 39; 41; 43; 44] estimates ranged from 0.33 to 1.35 cases of SUDEP annually per 1000 people with epilepsy. Two community-based studies limited to children[40; 45] estimated lower annual rates of 0.20 and 0.43 per 1000.

Nine clinic-based studies, mainly representing people with treatment-resistant epilepsy, yielded higher estimates of SUDEP occurrence, ranging from 1.2 to 6.3 cases of SUDEP annually per 1000 individuals.[23; 33; 37; 46-51]

Risk of death from status epilepticus among people with epilepsy. We found one class 1[15] and three class 3 studies,[37; 39; 50] all from the United Kingdom, describing the occurrence of fatal status epilepticus (Supporting Table 8). Two population-based studies, one encompassing all ages[15] and the other encompassing children only,[39], yielded estimated annual rates of 0.1 and 0.2 cases per 1000 persons with epilepsy,

respectively. A study of children with epilepsy enrolled in a residential school for learning disabilities yielded an annual rate of 1.0 cases per 1000 children.[50] Another study of people with epilepsy treated in a tertiary referral center yielded an annual rate of 0.4 cases per 1000 attendees.[37] Across these four studies, 1.9% of all deaths were attributed to status epilepticus.

Risk of fatal injury. As summarized in Table 3, ~~four~~ six studies described the risk of death from injuries among people with epilepsy.[11; 23; 24; 27; 52; 53] In ~~two~~ four studies there were ~~substantial~~ signficant elevations in the overall risk from all causes of injuries, one showing an adjusted odds ratio (aOR) of 3.6,[52] and ~~an SMR of~~ others showing SMRs ranging from 2.0 to 5.6.[11; 24; 27] Especially high risk estimates were found for drowning (or submersion or suffocation injuries), with SMRs ranging from 2.~~1~~0 to 13.8, and an aOR of 7.7.[11; 23; 24; 27; 52; 53] The risk of death from falls was also high, with an SMR of 4.6 and an aOR of 8.5. The elevated risk of suicide was also noteworthy, with SMRs of 2.6 to 5.0[11; 23; 24; 27] and an aOR of 3.7.[52]

Risk of death by categories of disease. As summarized in Table 4, ~~five~~ seven studies described risks of death attributable to broad disease categories.[9; 11; 14; 16; 17; 23; 24] Most of these studies showed that among people with epilepsy there were significantly increased risks of death due to neoplasia, cerebrovascular disease, and respiratory disease. Two studies also found an increased risk of death due to digestive diseases.[17; 24] Estimates pertaining to cardiovascular disease tended to show a smaller elevation of risk that were not statistically significant in the majority of the studies.

Discussion

Limitations. Our assessments of the quality of evidence of these studies are an attempt to set minimum standards for their likely validity. The criteria we applied emphasize methods addressing sensitivity of case ascertainment, accuracy of diagnoses, and representativeness. Inevitably, review processes such as ours involve qualitative judgments by reviewers, whose interpretations of study methods and applications of quality criteria are often not fully consistent: 50 percent of paired initial ratings were discordant, requiring reconsideration by the reviewers to achieve consensus.

Our criteria for assessing quality of evidence did not address the problem of confounding, a source of bias in studies measuring risks associated with specific factors. Confounding results from a mixing of effects of two or more causal risk factors that determine the measured outcome. Among the studies we reviewed, there are many potential confounders. For example, measurement of the risk of death by whether seizures are fully controlled or not (refractoriness) is potentially confounded by age, the types of seizures experienced (generalized tonic-clonic versus others), the underlying cause of epilepsy, and the presence of other comorbid conditions that may contribute to mortality. Some studies we reviewed reduced the effect of confounders through methods involving stratification or multivariate analysis; others did not.

The populations of these studies varied greatly. Community population-based studies were more likely to be representative of the general population of people with epilepsy, but results from the specific populations of these studies may not be fully generalizable to other populations of developed countries, where factors such as the occurrence of

epilepsy, medical care for epilepsy, general health care availability, and preventive public health practices vary. Studies of clinical cohorts that were not population-based vary much more in the extent to which their findings can be generalized. Some represented a relatively broad distribution of epilepsy cases by cause and severity; others predominantly represented epilepsy cases with seizures resistant to treatment or accompanied by substantial comorbidities.

Finally, our search strategy included general terms encompassing epilepsy-related mortality, but not terms for many specific causes, e.g., suicide. Thus, it is possible that some studies focused solely on such specific causes—if not indexed more generally to mortality in databases we searched—may have been overlooked in our review.

Interpretation. Despite these limitations, several implications of this review are clear. Our findings, now obtained by means of a systematic, evidence-based review, confirm and strengthen the conclusions of previous reviews, indicating a significantly increased risk of premature mortality among the general population of people with epilepsy—more than two-fold, as measured across all age groups by standardized mortality ratios. Comparative risks of premature death from epilepsy by these measurements appear slightly higher in males than females and appear substantially greater in younger age groups.

Mortality risk by age deserves further consideration. High elevations of risk among people with epilepsy (SMR roughly seven-fold) are seen through the fourth or fifth decade of life; thereafter, the risks measured in relation to the general population appear to decline markedly as risks of competing causes of death rise for all people.

These standardized mortality ratios should, however, not be interpreted as indicating that the absolute risk of deaths associated with epilepsy (that is, deaths from epilepsy, its underlying conditions, or its consequences) decline among older adults. The actual rates of death from these causes cannot be deduced from SMRs.

Several disease characteristics increase the risk of premature mortality among people with epilepsy. Epilepsy causes categorized as structural/metabolic ('symptomatic') carry a higher risk than causes classified as genetic ('idiopathic') or unknown ('cryptogenic'). Within the structural/metabolic category, specific etiologic comorbidities indicating static or progressive encephalopathies acquired congenitally or in early childhood indicate an especially high risk, as do brain tumors. People with epilepsy whose seizures do not fully remit under treatment and those with convulsions also carry a higher risk.

SUDEP is an important cause of death. The studies of SUDEP that we reviewed have serious limitations involving either case under-ascertainment or uncertainties in the prevalence of epilepsy in their populations, making it difficult to provide a summary estimate of its incidence. Taking these limitations into account, it appears likely that the annual rate of SUDEP exceeds 1 case per 1000 people with epilepsy. Among those whose seizures are not fully controlled, the rate appears several-fold higher. In general, the rate appears lower in children. While beyond the scope of this review, more extensive explorations of SUDEP risk factors and incidence are found in other recent reviews.[54-56]

Finally, injuries—both unintentional and intentional—are important causes of premature death among people with epilepsy. Further research is needed to better characterize these risks. Nevertheless, existing evidence indicates significantly elevated risks in particular for drowning, falls, and suicide.

Implications. Epilepsy-associated mortality imposes a significant burden on public health, and many of the specific causes of death associated with epilepsy—especially injuries, status epilepticus, and SUDEP—may be preventable. Accordingly, health care providers, researchers, and public health professionals should give high priority and sufficient resources toward prevention efforts directed to these causes. Health care systems should also ensure that all people with epilepsy have access as needed to high quality services, including access to specialty care, education, and social support services. By serving to promote the best possible seizure control, as well as the reduction of medical and psychiatric comorbidities and their consequences, many premature deaths among people with epilepsy may be prevented.

To this end, taking into account the limitations of evidence identified in this review, additional epidemiologic studies are needed as well as the development of methods and systems for long-term surveillance of mortality in people with epilepsy. These can promote advances in prevention strategies, enable evaluations of applied prevention interventions, and elucidate population trends over time. Such new studies and surveillance systems should be designed in conformity with current guidelines,[57] with careful attention to: (a) the representativeness of study populations, (b) accuracy in identifying all epilepsy and unprovoked seizure diagnoses among decedents, and (c)

accuracy in identifying all deaths and their specific causes among people with epilepsy. These studies and systems should also identify specific epilepsy characteristics and comorbidities that potentially increase risk of death. In sum, such epidemiologic studies and surveillance systems can enable future progress in reducing the public health burden of these premature deaths.

Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosures

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Supporting Information

Additional information can be found in the online version of this article.

Supporting Tables 1a and 1b. Detailed search strategy, inclusion criteria, and criteria for assessing strength of evidence.

Supporting Table 2. All-cause mortality among people with epilepsy by sex.

Supporting Table 3. All-cause mortality among people with epilepsy by age.

Supporting Table 4. Standardized mortality ratios by seizure type.

Supporting Table 5. Standardized mortality ratios by epilepsy etiology.

Supporting Table 6. Mortality among study subjects with seizures refractory to treatment

Supporting Table 7. Risk of SUDEP

Supporting Table 8. Risk of death from status epilepticus among people with epilepsy.

Tables and Figures

Table 1. Overall Mortality Risk among People with Epilepsy: All-age or Adult-only Populations

Study	Class	Locality	Pop'n Characteristic	Cohort Size*	Follow-up (years)	SMR	95% CI
Population- or community-based studies, all ages or adults only							
Lhatoo 2001[15]	1	England & Wales, UK	Incident cohort, all ages	792	11.8†	2.1	1.8-2.4
Lindsten 2000[16]	1	Vasterbotten Co., Sweden	Incident cases, adult cohort	107	10	2.5	1.2-3.2
Hauser 1980[14]	1	Rochester, MN, US	Incident cases, all ages	618	13.3†	2.3	1.9-2.6
Benn 2008[13]	2	Northern Manhattan, US	Incident epilepsy or unprovoked seizures, all ages	209	2.9†	1.7	1.1-2.3
Cockerell 1997[8]	2	UK	Incident cases, all ages	792	≤9	3.0	2.5-3.7
Morgan 2002[17]	2	Cardiff & Glamorgan, UK	Prevalent cases, all ages	3007	≤4	2.1	1.7-2.6
Olafsson 1998[18]	2	Iceland	Incident unprovoked seizures, all ages	224	≤30	1.6	1.2-2.2
Neligan 2011[10‡]	2	UK	Incident cases, all ages	564	22.8	2.6	2.2-3.0
Rakitin 2011[19]	2	Estonia	Incident cases, age ≥20 years	81	12.5†	2.6	1.8-3.5
Population- or community-based studies, children only							
Sillanpaa 2010[22]	1	Turku, Finland	Incident & prevalent cases, onset <16 y	245	40	6.4	5.9-7.0
Nickels 2012[21]	1	Rochester, MN, US	Incident cases, <18 y	467	7.9†	6.9	
Camfield 2002[20]	2	Nova Scotia, Canada	Incident cases <17 y	692	13.9†	7.5	4.4-13.0
Clinic-based studies, all ages or adults only							
Nilsson, 1997[24]	3	Stockholm, Sweden	Previously hospitalized for epilepsy	9061	≤17	3.6	3.5-3.7
Mohanraj 2006[23]	3	Glasgow, UK	Incident clinic referral cases	890	7†	1.4	1.2-1.7
			Prevalent clinic referral cases	2689	7†	2.0	1.8-2.3
Trinka 2013[12]	3	Tyrol, Austria	Cohort of attendees of epilepsy referral clinic	3334	~~28.1~~≤29	2.2	2.0-2.4
Granbichler 2015[11§]	3	Tyrol, Austria	Cohort of adult attendees of epilepsy referral clinic	4295	≤39	1.7	(1.6-1.9)
Clinic-based studies, children only							
Callenbach 2001[26]	3	Netherlands	Incident cases	472	5.0	7.0	2.4-11.5
Berg 2004[25]	3	Connecticut, US	Incident cases <16 y representative sample	613	7.9	7.5	4.4-13.0

* Number of persons with epilepsy followed
† Median or mean follow-up period
‡ Extended follow-up of cohort described in Cockerell 1997.
§ Extended follow-up and expansion of cohort described in Trinka 2013.

Table 2. Mortality by comorbid brain disorder

Study	Class	Country	Cases	Follow-up	Measure	Comorbid Condition				
						Enceph	MR/CP	Brain Tumor	CVD	Dementia
Lhatoo 2001[15]	1	United Kingdom	Incident	11.8	SMR HR	25	 10.9	 12.0	 2.4	
Nickels 2012[21]	1	United States	Incident, children	7.9	HR	12.8				
Camfield 2002[20]	2	Canada	Incident, children	13.9	HR	22.0				
Cockerell 1997[8]	2	United Kingdom	Incident	≤9.0	SMR	50				
Forsgren 1996[30]	2	Sweden	Prevalent, Age 0-19 All ages	 ≤7.0 6.6	 SMR SMR		 52.0 5.8			
Hauser 1980[14]		United States	Incident	13.3	SMR	11.0				
Neligan 2011[10]*	2	United Kingdom	Incident	22.8	SMR	18.6				
Keezer 2016[9]*	2	United Kingdom	Incident	23	HR			5.0	4.0	2.8
Berg 2013[32]	2	International	Incident, children	13.6	Rate	7.3				
Berg 2004[25]	3	United States	Incident, children	7.9	SMR	33.5				
Callenbach 2001[26]	3	Netherlands	Incident, children	5.0	SMR	22.9				
Loiseau 2005[31]	3	France	Incident	≤1.0	SMR			41.5		5.4
Granbichler 2015[11]	3	Austria	Prevalent	≤39	SMR				2.6	

Notes
Follow-up refers to median or mean duration of subject follow-up in years, reported or calculated from report data. If not calculable, '≤' signifies maximum duration of subject follow-up.
Abbreviations: 'Enceph' – static or progressive encephalopathies, including major congenital or acquired central nervous system deficits, not specifically defined; 'MR/CP' – mental retardation (intellectual disability) or cerebral palsy; CVD – cerebrovascular disease.
Hazard ratios (HRs) compare persons with epilepsy and comorbid condition with persons with epilepsy and not comorbid condition.
Rate is number of deaths per year among 1000 children with epilepsy and comorbid condition.
Lower limit of confidence interval exceeds 1.0 for all SMRs and HRs reported.
*Follow-up reports of cohort described in Cockerell 1997.

Table 3. Risk of death from injury among people with epilepsy

Study	Class	Locality	Cohort	External Cause	Risk Measure	Risk Estimate (95% C.I.)
All Injuries						
Fazel 2013[52]	3	Sweden	Population-based	All	aOR	3.6 (3.3–4.0)
Nilsson 1997[24]	3	Sweden	Prior epilepsy hospitalization	All	SMR	5.6 (5.0-6.3)
Rafnsson 2001[27]	2	Iceland	Population-based, incident unprovoked seizures	All	SMR	2.6 (1.6-6.5)[a]
Granbichler 2015[11]	3	Austria	Hospital-based	All	SMR	2.0 (1.6-2.5)
Unintentional Injuries						
Diekema 1993[53]	2	United States	Population-based, children	Drowning	SMR	13.8 (7.0-27.0)
Granbichler 2015[11]	3	Austria	Hospital-based	Transport Submersion/ suffocation	SMR SMR	1.3 (0.6-2.5) 2 (0.7-4.3)
Fazel 2013[52]	3	Sweden	Population-based	Drowning Vehicle Fall	aOR aOR aOR	7.7 (4.7–12.7) 1.4 (1.1–1.8) 8.5 (5.3–13.7)
Mohanraj 2006[23]	3	United Kingdom	Epilepsy referral center, incident cases	All accidents	SMR	4.8 (2.2–9.1)
Nilsson 1997[24]	3	Sweden	Prior epilepsy hospitalization	Submersion/ suffocation Transport Falls Fire/flame	SMR SMR SMR SMR	8.2 (5.2-12.1) 1.8 (0.9-3.4) 4.6 (3.5-5.8) 10.3 (5.8-17.0)
Intentional Injuries						
Fazel 2013[52]	3	Sweden	Population-based	Suicide Assault	aOR aOR	3.7 (3.3–4.2) 2.8 (1·6–4.8)
Granbichler 2015[11]	3	Austria	Hospital-based	Suicide	SMR	4.2 (2.0-8.1)
Mohanraj 2006[23]	3	United Kingdom	Epilepsy referral center, incident cases	Suicide	SMR	2.6 (0.5-7.5)
Nilsson 1997[24]	3	Sweden	Prior epilepsy hospitalization	Suicide	SMR	3.5 (2.6-4.6)
Rafnsson 2001[27]	2	Iceland	Population-based, incident unprovoked seizures	Suicide	SMR	5.0 (1.3-12.8)[a]

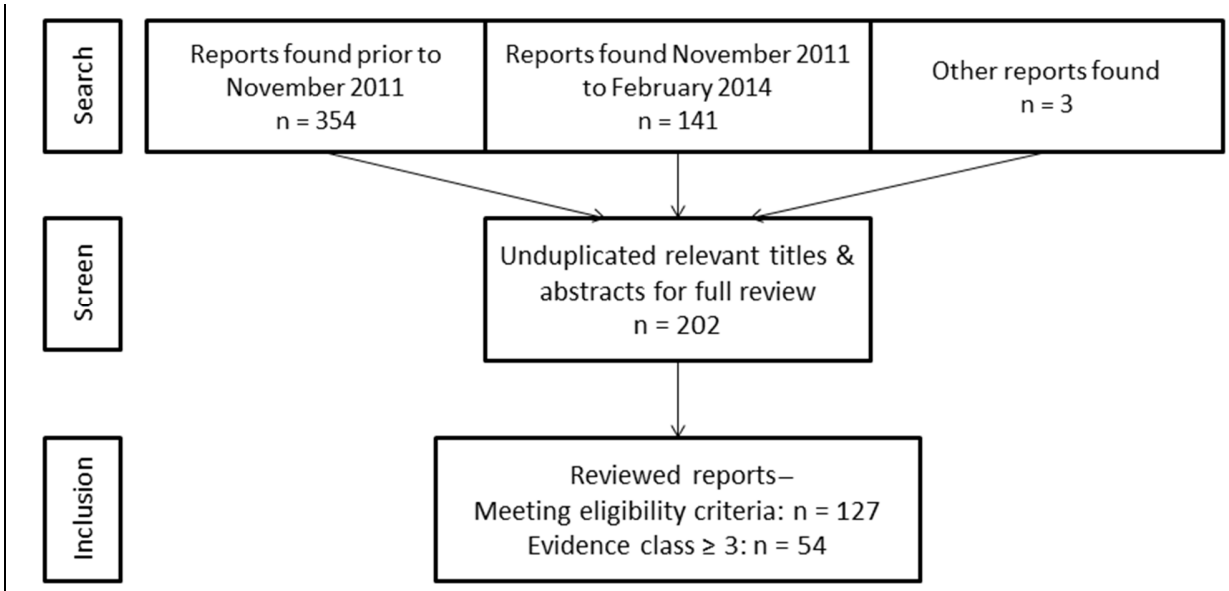
Notes:
aOR refers to adjusted odds ratios for people with epilepsy compared to age- and sex-matched controls.
[a] Recalculated to combine data for men and women.

Table 4. Risk of death among people with epilepsy by category of disease causing death.

Study	Class	Country	Cohort	Risk Measure	~~Standardized Mortality Ratios~~Risk Estimate by Cause				
					Neoplasia	CVD	Cerebrovasc	Digestive	Respiratory
Hauser, 1980[14]	1	United States	Incident	SMR	2.9 (2.1-3.9)	1.1 (0.8-1.5)	2.6 (1.8-3.6)		3.5 (1.6-6.6)
Lindsten, 2000[16]	1	Sweden	Incident	SMR	3.4 (1.9-5.8)	1.8 (1.2-3.0)	4.2 (2.2-8.0)		
Keezer, 2016[6]	2	United Kingdom	Incident	HR	4.2 (2.3–7.9)		4.0 (2.0-8.0)		
Morgan, 2002[17]	2	United Kingdom	Prevalent	SMR	1.5 (1.1-1.8)	1.2 (0.9-1.5)	2.7 (2.0-3.3)	2.4 (1.3-3.5)	1.7 (1.3-2.2)
Nilsson, 1997[24]	3	Sweden	Prevalent	SMR	2.6(2.4-2.8)	3.1 (3.0-3.3)		5.1 (4.4-5.8)	4.0 (3.6-4.5)
Mohanraj, 2006[23]	3	United Kingdom	Incident	SMR	0.7 (0.4-1.2)	1.5 (0.9-2.3)	1.6 (0.8-2.9)		2.6 (1.5-4.0)
Granbichler, 2015[11]	3	Austria	Prevalent	SMR	1.2 (1.0-1.4	1.6 (1.3-1.8)	2.6 (2.1-3.1)	0.8 (0.3-1.6)	1.9 (1.4-2.5)

Notes
Abbreviations: ‘CVD’ – cardiovascular disease, ‘Cerebrovasc’ – cerebrovascular disease.
Parenthetic numbers denote 95% confidence intervals.

Figure 1. Results of systematic search.



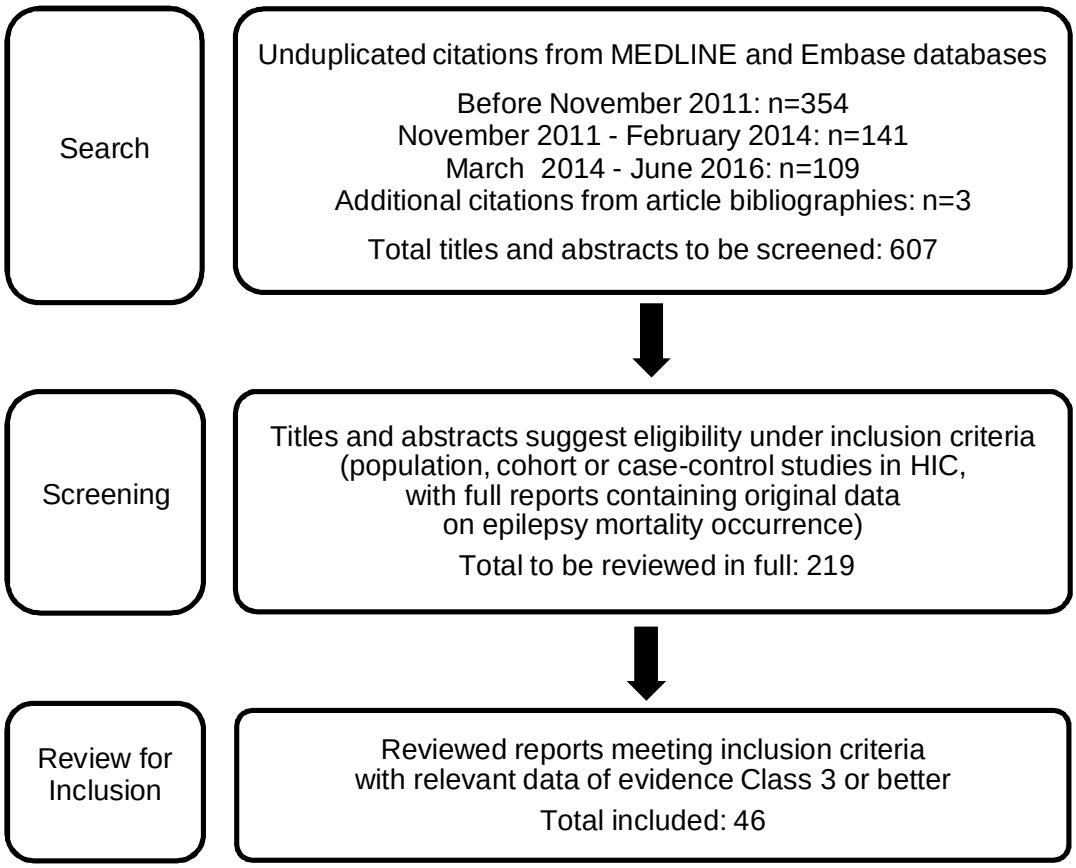
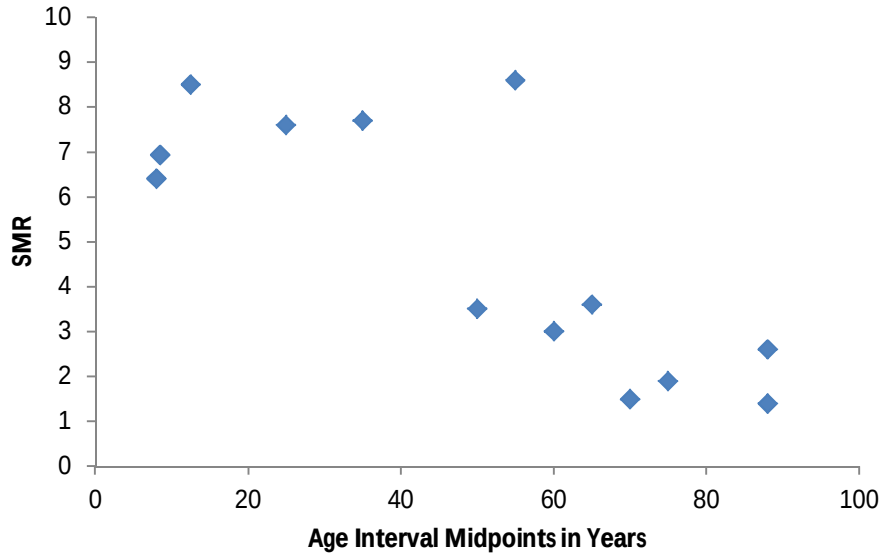
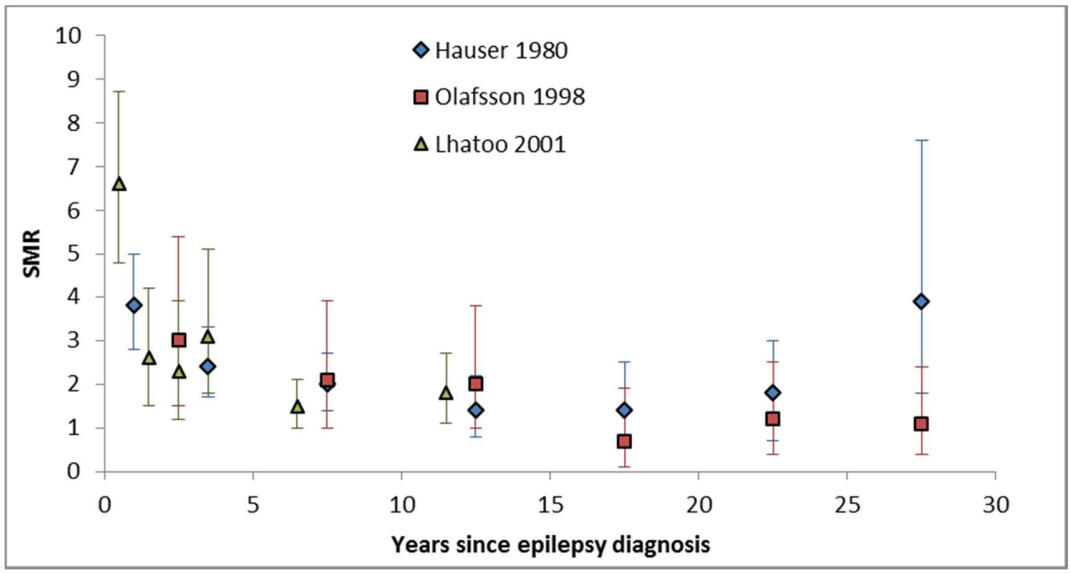


Figure 2. Standardized Mortality Ratios by Age: Deaths from All Causes Among People with Epilepsy



Source: Four class 1 and class 2 studies. [8; 14; 20; 22]

Figure 3. Standardized Mortality Ratios by Interval from Epilepsy Diagnosis*



*Data points represent the midpoint of intervals from diagnosis described in individual studies. Error bands indicate 95% confidence intervals.

Supporting Information

Supporting Table 1a. Search strategy and report screening criteria

Ovid® MEDLINE
Terms included any of the following Medical Subject Headings, with subheadings indicated by brackets and term combinations indicated by 'AND' used as a Boolean operator:

1. Epilepsy [epidemiology] AND Epilepsy [mortality]
2. Epilepsy AND Mortality
3. Epilepsy AND 'Sudden death' [epidemiology]
4. Epilepsy AND Death [etiology]
5. Epilepsy AND 'Wounds and Injuries' (and subheadings) [mortality]
6. 1 OR 2 OR 3 OR 4 OR 5

Search limited to human studies.

Embase®

1. 'epilepsy'/mj AND ([article]/lim OR [review]/lim) AND [humans]/lim AND [embase]/lim AND [2014-2016]/py
2. 'mortality'/exp AND [2014-2016]/py
3. 'epidemiology'/exp AND [embase]/lim AND [2014-2016]/py
4. 1 and 2 and 3

Criteria required to accept articles for full review:

- Original reports providing new data including measures of mortality for people with epilepsy, e.g., mortality incidence rates, SMRs, proportionate mortality ratios, or other comparative risk ratios.
- Population- or community-based, clinical cohort, or case-control studies included.
- High-income country localities, as defined by World Bank.

Supporting Table 1b. Criteria for Assessing Strength of Evidence

Sensitivity of Epilepsy Case Ascertainment

- 1 = Screening methods appear likely to ascertain nearly all (≥ 85%) cases in population
- 2 = Screening methods appear likely to ascertain most (70 - 84%) cases in population
- 3 = Screening methods appear likely to ascertain majority (50 - 69%) of cases in population
- 4 = Screening methods appear unlikely to ascertain majority of cases in population OR information published is insufficient to assess
- N/A = Not applicable: not a population-based study or sensitivity of methods of epilepsy case ascertainment not relevant to quality of study.

Sensitivity of Mortality Case Ascertainment

- 1 = Fatalities appear likely to be recorded in nearly all (≥ 85%) cases in study population
- 2 = Fatalities appear likely to be recorded in most (70 - 84%) cases in study population
- 3 = Fatalities appear likely to be recorded in majority (50 - 69%) of cases in study population
- 4 = Fatalities appear unlikely to be recorded in majority of cases in study population OR information published is insufficient to assess

Accuracy of Diagnoses of Epilepsy

- 1 = Cases are diagnosed (or confirmed) by specialist clinician (i.e., with neurologic training), AND ILAE case definition applied
- 2 = Cases are often diagnosed by non-specialist clinician, OR minor deviation from ILAE case definition
- 3 = All or substantial proportion of cases diagnosed based on self-report or non-clinical sources with specified criteria judged to have fair positive predictive value
- 4 = All or substantial proportion of cases diagnosed with poorly defined criteria from non-clinical sources; positive predictive value judged to be poor OR information published is insufficient to assess

Accuracy of Diagnoses of Cause of Death

- 1 = Determined mainly from either autopsy, ~~ME~~ medical examiner/coroner investigation, or other clinical investigation (e.g., review of medical records, structured interview of survivors or "verbal autopsy")
- 2 = Determined largely or wholly from death certificate data, when such data are judged to have good positive predictive value for the specific causes of interest
- 3 = Determined largely or wholly from death certificate data, when such data are judged to have only fair positive predictive value for the specific causes of interest
- 4 = Other sources of data deemed to have poor positive predictive value for the causes of interest OR information published is insufficient to assess

Representativeness of the study population

- 1 = Cohort studies of incident epilepsy whose enrolled cases appear highly representative of the population of interest
- 2 = Studies of prevalent epilepsy whose enrolled cases appear highly representative of the population of interest
- 3 = Studies of epilepsy whose enrolled cases appear somewhat representative of the population of interest
- 4 = Studies of epilepsy whose enrolled cases appear poorly representative of the population of interest or where representativeness cannot be assessed.

Supporting Table 2. All-cause mortality among people with epilepsy by sex

Study	Class	Country	Pop'n Characteristic	SMR (95% CI)	
				Females	Males
Benn 2008[13]	2	United States	Incident epilepsy or unprovoked seizure	1.7 (1.0-2.5)	1.6 (0.8-2.8)
Hauser 1980[14]	1	United States	Incident epilepsy, idiopathic cause	1.6	2.1
Lindsten 2000[16]	1	Sweden	Incident cases, aged >16 years	2.3 (1.4-3.7)	2.7 (1.8-3.9)
Morgan 2002[17]	2	United Kingdom	Prevalent cases	2.0 (1.5-2.6)	2.3 (1.7-2.9)
Nilsson, 1997[24]	3	Sweden	Previous epilepsy hospitalization	3.4 (3.3-3.6)	3.7 (3.6-3.9)
Rafnsson, 2001[27]	2	Iceland	Incident epilepsy or unprovoked seizure	0.8 (0.4-1.5)	2.3 (1.6-3.1)
Trinka 2013[12]	3	Austria	Referrals to specialized clinic	1.9 (1.7-2.2)	2.4 (2.1-2.6)

Supporting Table 3. All-cause mortality among people with epilepsy by age

Author	Class	Country	Age in Years	SMR	CI
Risk Described by Age of Epilepsy Onset					
Berg 2004[25]	3	United States	<16	7.5	4.38-13.0
Callenbach 2001[26]	3	Netherlands	<16	7.0	2.4-11.5
Camfield 2002[20]	2	Canada	<17	6.9	
Lindsten 2000[16]	1	Sweden	15-39	9.5	3.1-29.4
			40-59	10.7	6.5-17.6
			60-79	2.4	1.6-3.8
			>80	1.3	0.7-2.4
Moseley 2013[28]	1	United States	<0.08*	46.4	12.7-119.3
			<1	22.3	9.6-43.8
			1- 17	5.67	2. 5-11.2
Risk Described by Age at Follow-up					
Cockerell 1997[8]	2	United Kingdom	0-49	7.6	4.2-12.5
			50-59	8.6	4.7-14.1
			60-69	3.6	2.2-5.5
			70-79	1.9	1.2-2.8
			>80	2.6	1.8-3.6
Hauser 1980[14]	1	United States	0-24	8.5	5.4-12.9
			25-44	7.7	5.1-11.0
			45-54	3.5	2.0-5.7
			55-64	3.0	2.0-4.5
			65-74	1.5	1.0-2.2
			>74	1.4	1.1-1.9
Nilsson 1997[24]	3	Sweden	15-34	14.4	12.4-16.7
			35-54	10.1	9.4-10.9
			55-74	4.0	3.9-4.2
			>74	2.1	2.0-2.3
Sillanpaa 2010[22]	1	Finland	<16	6.4	5.9-7.0

*Age of epilepsy onset <1 month.

Supporting Table 4. Standardized mortality ratios by seizure type

Study	Class	Country	Cases	Generalized	GTC	Partial
Lindsten 2000	1	Sweden	Incident cases (males)		3.9	2.1
Benn 2008	2	United States	Incident epilepsy and first unprovoked seizure	1.3		1.8
Rakitin 2011	2	Estonia	Incident cases (adults)		2.7*	1.5†

*Partial seizures with secondary generalization
†Simple partial seizures

Supporting Table 5. Standardized mortality ratios by epilepsy etiology

Study	Class	Country	Cryptogenic	Idiopathic	Crypt/Idio	Symptomatic
Hauser 1980[14]	1	US			1.8 (1.4-2.3)	2.2 (1.8-2.7)
Lhatoo 2001[15]	1	UK		1.3 (0.9-1.9)		3.7 (2.9-4.6)
Benn 2008[13]	2	US			0.9 (0.2–2.2)	2.3 (1.5–3.4)
Cockerell 1997[8]	2	UK		1.6 (1.0-2.4)		4.3 (3.3-5.5)
Neligan 2011[10]	2	UK			1.7 (1.3-2.1)	3.7 (3.1-4.4)
Olafsson 1998[18]	2	Iceland	1.3 (0.8-1.9)			2.3 (1.4-3.5)‡ 4.1 (2.4-6.6)§
Rakitin 2011[19]	2	Estonia	2.1 (1.1–3.6)			3.6 (2.3–5.2)
Mohanraj 2006[23]	3	UK	1.1 (0.7–1.6)	3.1 (0.9–7.8)		1.4 (1.1-1.8)
Trinka 2013[12]	3	Austria	1.7 (1.5-1.9)	2.1 (1.4-3.0)		2.8 (2.6-3.2)

Category abbreviations: Crypt/Idio – cryptogenic and idiopathic categories combined or not distinguished;

‡15-year follow-up
§≤30-year follow-up

Supporting Table 6. Mortality among study subjects with seizures refractory to treatment

Study	Class	Country	Cohort	Rate/ 1000	SMR	RR	OR
Sillanpaa 1998[34]	1	Finland	Not seizure-free, onset age <16 years			9.3 (3.8-22.7)*	
Annegers 2000[33]	2	International	Receiving vagal nerve stimulation	7.9 (5.2-11.8)	3.6 (2.3-5.4)		
Ridsdale 2011[38]	2	UK	Not seizure-free				1.3 (1.2-1.4)*
Sperling 2005[35]	2	United States	Post epilepsy surgery with recurrent seizures.	11.4 (7.0-18.3)		13.4 (1.8-100.6)*	
Vickrey 1997[36]	2	United States	Evaluated for epilepsy surgery			4.3 (1.8-10.2)†	
Lip 1992[37]	3	UK	Referred to tertiary epilepsy center	7.3 (4.5-11.8)			
Trinka 2013[12]	3	Austria	Not seizure-free		2.4 (2.2-2.6)		

Notes:
Annual rates per 1000 persons with epilepsy. Numbers in parentheses refer to 95% confidence intervals.
*Comparison of people who are not seizure-free with those who are seizure-free.
†Comparison of experience following evaluation among people who are not surgically treated and those who are surgically treated.

Supporting Table 7. Risk of SUDEP

Study	Class	Country	Cohort	Rate (95% C.I.)
Community-based studies				
Ficker 1998[41]	2	Rochester, MN, US	Prevalent	0.35 (0.17-0.68)
Ackers 2011[39]	3	UK	Prevalent	0.33 (0.15-0.64)
Donner 2001[40]	3	Canada	Prevalent, <18 years of age	0.20 (0.13-0.29)
Holst 2013[42]	3	Denmark	Prevalent, ≤35 years of age	0.41 (0.31-0.55)
Opeskin 2003[43]	3	Victoria, Australia	Prevalent[a]	1.28 (0.96-1.70)
Mohanraj 2006[23]	3	Glasgow, UK	Incident	1.08 (0.47-2.33)
Tennis 1995[44]	3	Saskatchewan, Canada	Prevalent[a]	0.54 (0.33-0.87) 1.35[b] (1.00-1.83)
Weber 2005[45]	3	Basel, Switzerland	Prevalent, children	0.43 (0.14-1.18)
Clinic-based studies				
Nilsson 2003[48]	1	Sweden	Refractory epilepsy, not eligible for surgery	6.3 (1.7-16.1)
Annegers 2000[33]	2	International	Vagus nerve stimulation cohort	4.1 (2.3-7.2)
Derby 1996[46]	2	UK	Refractory epilepsy	1.5 (0.8-2.7)
Timmings 1998[49]	2	Cardiff, UK	Referrals to outpatient clinic	2.0 (1.1-3.4)
Lip 1992[37]	3	Glasgow, UK	Refractory epilepsy	4.9 (2.6-8.8)
Mohanraj 2006[23]	3	Glasgow, UK	Referrals to outpatient clinic	2.4 (1.8-3.2)
Nashef 1995[50]	3	UK	School for learning disability	3.4 (1.9-5.8)
Nashef 1995[47]	3	UK	Referrals to outpatient clinic	5.9 (3.1-11.0)
Walczak 2001[51]	3	Minneapolis, MN, US	Referral to outpatient clinic	1.2 (0.8-1.9)

Annual rate per 1000 persons with epilepsy
[a]Based on estimated population of people with epilepsy
[b]Estimate adjusted for sensitivity

Supporting Table 8. Risk of Death from Status Epilepticus among People with Epilepsy

Study	Class	Locality	Cases	Rate/1000	
Lhatoo 2001	1	United Kingdom	Population-based, all ages	0.09	0.005-0.57
Ackers 2011	3	United Kingdom	Population-based, children	0.22	0.09-0.51
Lip 1992	3	United Kingdom	Refractory epilepsy	0.41	0.02-2.63
Nashef 1995	3	United Kingdom	School for learning disability	0.97	0.03-2.66