



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

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 reevaluate and quantify the risks, potential risk factors, and causes of these deaths. 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. 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 <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 (SUDEP), status epilepticus, unintentional injuries, and suicide. 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 healthcare providers, researchers, and public health professionals.

KEY WORDS: Seizures, Convulsions, Death, Developed countries, Resource-rich countries, Premature mortality.



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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

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. They 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 attributed mainly 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 in the preceding 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 reevaluate 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 premature mortality in epilepsy. This review focuses on mortality in high-income

countries (HICs); 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 1,000 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 a more detailed account of individual subject survival time, using regression modeling.⁷

The standardized mortality ratio (SMR) is the 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, 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:

- 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]

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, for example, mortality incidence rates, SMRs, proportionate mortality ratios, and 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 that 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 Table S1A.

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:

- 1 sensitivity of epilepsy case ascertainment,
- 2 sensitivity of mortality case ascertainment,
- 3 accuracy of diagnoses of epilepsy,
- 4 accuracy of diagnoses of cause of death,
- 5 representativeness of the study population.

We assigned each report to categories designated as class 1 through class 4, representing strongest through 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 Table S1B.

FINDINGS

Search results

Searches of Medline and Embase conducted in November 2011 and updated in February 2014 and June 2016, in sum, yielded 607 article citations. Results of the search and screening are detailed in Figure 1. A total of 46 reports met all inclusion criteria with strength of evidence rated \geq “class 3,” representing high-income countries. Three reports represented different findings over time from a

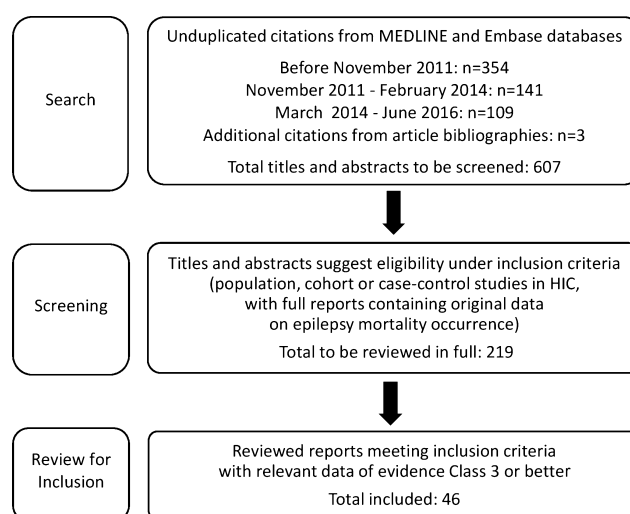


Figure 1. Results of systematic search. Flowchart describes search process. *Epilepsia* © ILAE

single cohort from the United Kingdom^{8–10} and two reports from a single cohort in Austria,^{11,12} but 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 six 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.

Four clinic- or hospital-based cohort studies of people with epilepsy, 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

Table S2 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 Table S3.^{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

Table 1. Overall mortality risk among people with epilepsy: all-age or adult-only populations

Study	Class	Locality	Population characteristic	Cohort size ^a	Follow-up (years)	SMR	95% CI
Population- or community-based studies, all ages or adults only							
Lhatoo (2001) ¹⁵	1	England and Wales, United Kingdom	Incident cohort, all ages	792	11.8 ^b	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, U.S.A.	Incident cases, all ages	618	13.3 ^b	2.3	1.9–2.6
Benn (2008) ¹³	2	Northern Manhattan, U.S.A.	Incident epilepsy or unprovoked seizures, all ages	209	2.9 ^b	1.7	1.1–2.3
Cockerell (1997) ⁸	2	United Kingdom	Incident cases, all ages	792	≤9	3.0	2.5–3.7
Morgan (2002) ¹⁷	2	Cardiff and Glamorgan, United Kingdom	Prevalent cases, all ages	3,007	≤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,c}	2	United Kingdom	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 ^b	2.6	1.8–3.5
Population- or community-based studies, children only							
Sillanpaa (2010) ²²	1	Turku, Finland	Incident and prevalent cases, onset <16 years	245	40	6.4	5.9–7.0
Nickels (2012) ²¹	1	Rochester, MN, U.S.A.	Incident cases, <18 years	467	7.9 ^b	6.9	
Camfield (2002) ²⁰	2	Nova Scotia, Canada	Incident cases <17 years	692	13.9 ^b	7.5	4.4–13.0
Clinic-based studies, all ages or adults only							
Nilsson (1997) ²⁴	3	Stockholm, Sweden	Previously hospitalized for epilepsy	9,061	≤17	3.6	3.5–3.7
Mohanraj (2006) ²³	3	Glasgow, United Kingdom	Incident clinic referral cases	890	7 ^b	1.4	1.2–1.7
			Prevalent clinic referral cases	2,689	7 ^b	2.0	1.8–2.3
Trinka (2013) ¹²	3	Tyrol, Austria	Cohort of attendees of epilepsy referral clinic	3,334	≤29	2.2	2.0–2.4
Granbichler (2015) ^{11,d}	3	Tyrol, Austria	Cohort of adult attendees of epilepsy referral clinic	4,295	≤39	1.7	1.6–1.9
Clinic-based studies, children only							
Callenbach (2001) ²⁶	3	The Netherlands	Incident cases	472	5.0	7.0	2.4–11.5
Berg (2004) ²⁵	3	Connecticut, U.S.A.	Incident cases <16 years representative sample	613	7.9	7.5	4.4–13.0

^aNumber of persons with epilepsy followed.
^bMedian or mean follow-up period.
^cExtended follow-up of cohort described in Cockerell et al.⁸
^dExtended follow-up and expansion of cohort described in Trinka et al.¹²

younger than 45 years (range 6.4–8.5), whereas comparatively lower SMR elevations were reported in age groups older than 64 years (range 1.4–2.6). 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 (Fig. 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

versus idiopathic or cryptogenic epilepsy, the early elevation of mortality risk after diagnosis was observed mainly 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 seizure¹³ provided estimates of risk according to the type of seizures experienced by their subjects as listed in Table S4. For those with generalized tonic–clonic seizures, a Swedish study¹⁶ 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 study¹⁹ reported an SMR of 2.7, compared to an SMR of 1.5 for subjects with simple partial seizures. For

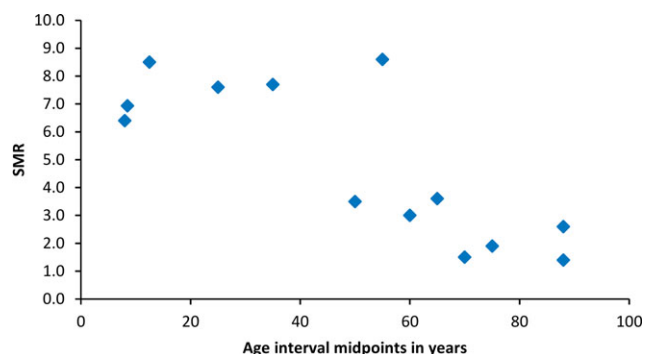


Figure 2. Standardized mortality ratios by age: Deaths from all causes among people with epilepsy. Data points represent findings from four class 1 and class 2 studies.^{8,14,20,22}
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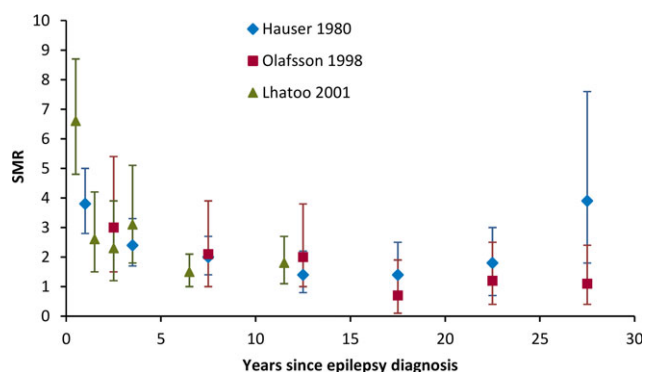


Figure 3. Standardized mortality ratios by interval from epilepsy diagnosis. Data points represent the midpoint of intervals from diagnosis described in individual studies. Error bands indicate 95% confidence intervals.
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those with focal seizures not 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 Table S5 reported SMRs according to these broad categories of cause of epilepsy: cryptogenic, idiopathic, or symptomatic. 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. 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 2.2–4.3. 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 13 studies that assessed the risk of death among subjects with comorbid neurologic conditions 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.

Risk in people still having seizures under treatment

Seven cohort studies summarized in Table S6 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. 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 Table S7, SUDEP occurrence in general populations of people with epilepsy was addressed by eight community-based studies,^{23,39–45} 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 1,000 people with epilepsy. Two community-based studies limited to children^{40,45} estimated lower annual rates of 0.20 and 0.43 per 1,000.

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 1,000 individuals.^{23,33,37,46–51}

Risk of death from status epilepticus among people with epilepsy

We found one class 1¹⁵ and three class 3 studies,^{37,39,50} all from the United Kingdom, describing the occurrence of

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	25				
					HR		10.9	12.0	2.4	
Nickels (2012) ²¹	1	U.S.A.	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	≤7.0	SMR		52.0			
			All ages	6.6	SMR		5.8			
Hauser (1980) ¹⁴		U.S.A.	Incident	13.3	SMR	11.0				
Neligan (2011) ^{10,a}	2	United Kingdom	Incident	22.8	SMR	18.6				
Keezer (2016) ^{9,a}	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	U.S.A.	Incident, children	7.9	SMR	33.5				
Callenbach (2001) ²⁶	3	The 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	

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.

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. 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 1,000 children with epilepsy and comorbid condition. Lower limit of confidence interval exceeds 1.0 for all SMRs and HRs reported.

^aFollow-up reports of cohort described in Cockerell et al.⁸

fatal status epilepticus (Table S8). Two population-based studies, one encompassing all ages¹⁵ and the other encompassing children only,³⁹ yielded estimated annual rates of 0.1 and 0.2 cases per 1,000 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 1,000 children.⁵⁰ Another study of people with epilepsy treated in a tertiary referral center yielded an annual rate of 0.4 cases per 1,000 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, six studies described the risk of death from injuries among people with epilepsy.^{11,23,24,27,52,53} In four studies there were significant elevations in the overall risk from all causes of injuries, one showing an adjusted odds ratio (aOR) of 3.6,⁵² and 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 2.0 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 2.6–5.0^{11,23,24,27} and an aOR of 3.7.⁵²

Risk of death by categories of disease

As summarized in Table 4, 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 was 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% 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

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

Study	Class	Locality	Cohort	External cause	Risk measure	Risk estimate (95% CI)
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	U.S.A.	Population-based, children	Drowning	SMR	13.8 (7.0–27.0)
Granbichler (2015) ¹¹	3	Austria	Hospital-based	Transport	SMR	1.3 (0.6–2.5)
				Submersion/suffocation	SMR	2 (0.7–4.3)
Fazel (2013) ⁵²	3	Sweden	Population-based	Drowning	aOR	7.7 (4.7–12.7)
				Vehicle	aOR	1.4 (1.1–1.8)
				Fall	aOR	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	SMR	8.2 (5.2–12.1)
				Transport	SMR	1.8 (0.9–3.4)
				Falls	SMR	4.6 (3.5–5.8)
				Fire/flame	SMR	10.3 (5.8–17.0)
Intentional injuries						
Fazel (2013) ⁵²	3	Sweden	Population-based	Suicide	aOR	3.7 (3.3–4.2)
				Assault	aOR	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

aOR refers to adjusted odds ratios for people with epilepsy compared to age- and sex-matched controls.
^aRecalculated 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	Risk estimate by cause				
					Neoplasia	CVD	Cerebrovasc	Digestive	Respiratory
Hauser (1980) ¹⁴	1	U.S.A.	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) ⁹	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)

CVD, cardiovascular disease; Cerebrovasc, cerebrovascular disease.
 Parenthetic numbers denote 95% confidence intervals.

experienced (generalized tonic-clonic vs. 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, for example, 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 twofold, as measured across all age groups by SMRs. 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 sevenfold) 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) declines 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 underascertainment 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 one case per 1,000 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. Although 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, healthcare providers, researchers, and public health professionals should give high priority and sufficient resources toward prevention efforts directed to these causes. In addition, healthcare systems should 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 the following: (1) the representativeness of study populations, (2) accuracy in identifying all epilepsy and unprovoked seizure diagnoses among decedents, and (3) accuracy in identifying all deaths and their specific causes among people with epilepsy. In addition, these studies and systems should 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.

DISCLOSURE OF CONFLICT OF INTEREST

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DISCLAIMER

This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of ILAE.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. (A, B) Detailed search strategy, inclusion criteria, and criteria for assessing strength of evidence.

Table S2. All-cause mortality among people with epilepsy by sex.

Table S3. All-cause mortality among people with epilepsy by age.

Table S4. Standardized mortality ratios by seizure type.

Table S5. Standardized mortality ratios by epilepsy etiology.

Table S6. Mortality among study subjects with seizures refractory to treatment.

Table S7. Risk of SUDEP.

Table S8. Risk of death from status epilepticus among people with epilepsy.