RESEARCH ARTICLE

Epilepsy-Related Mortality in Children and Young Adults in Denmark

A Nationwide Cohort Study

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Abstract

Background and Objectives

Mortality is increased in epilepsy, but the important issue is that a proportion of epilepsy-related death is potentially preventable by optimized therapy and therefore needs to be identified. A new systematic classification of epilepsy-related mortality has been suggested to identify these preventable deaths. We applied this classification to an analysis of premature mortality in persons with epilepsy who were <50 years of age.

Methods

The study was a population-based retrospective cohort of all Danish citizens with and without epilepsy 1 to 49 years of age during 2007 to 2009. Information on all deaths was retrieved from the Danish Cause of Death Registry, autopsy reports, death certificates, and the Danish National Patient Registry. The primary cause of death in persons with epilepsy was evaluated independently by 3 neurologist, 1 neuro-pediatrician, and 2 cardiologists. In case of uncertainty, a pathologist was consulted. All deaths were classified as either epilepsy related or not epilepsy related, and the underlying causes or modes of death were compared between persons with and without epilepsy.

Results

During the study period, 700 deaths were identified in persons with epilepsy, and 440 (62.9%) of these were epilepsy related, 169 (38%) directly related to seizures and 181 (41%) due to an underlying neurologic disease. Sudden unexpected death in epilepsy accounted for 80% of deaths directly related to epilepsy. Aspiration pneumonia was the cause of death in 80% of cases indirectly related to epilepsy. Compared with the background population, persons with epilepsy had a nearly 4-fold increased all-cause mortality (adjusted mortality hazard ratio 3.95 [95% confidence interval [CI] 3.64–4.27], $p < 0.0001$) and a higher risk of dying of various underlying causes, including alcohol-related conditions (hazard ratio 2.91 [95% CI 2.23–3.80], $p < 0.0001$) and suicide (hazard ratio 2.10 [95% CI 1.18–3.73], $p = 0.01$).

Discussion

The newly proposed classification for mortality in persons with epilepsy was useful in an unselected nationwide cohort. It helped in classifying unnatural causes of death as epilepsy related or not and in identifying potentially preventable deaths. The leading causes of premature mortality in persons <50 years of age were related to epilepsy and were thus potentially preventable by good seizure control.

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Glossary

ASM = antiseizure medication; **ATC** = Anatomic Therapeutic Chemical; **CI** = confidence interval; **ICD** = *International Classification of Diseases*; **ILAE** = International League Against Epilepsy; **SUDEP** = sudden unexpected death in epilepsy.

Persons with epilepsy have an increased risk of premature death. Despite huge efforts to understand potentially preventable mechanisms, the risk has not declined over time.[1-4]

Compared with the general population, the overall mortality rate in persons with epilepsy is 2- to 4-fold higher and highest in the young.[1,3] In persons <50 years of age, the risk of death is 7-fold higher, while it is up to 22-fold higher in children.[3,5,6]

Many different causes of death contribute to this elevated risk. Some are directly related to seizures such as sudden unexpected death in epilepsy (SUDEP), status epilepticus, drowning, or lethal accidents. Other are indirectly related to epilepsy such as adverse effects of therapy or an underlying neurologic disease such as brain tumors. Some epilepsy-related deaths might be prevented by optimizing therapy and should therefore be identified.

During recent years, interest has focused on SUDEP, and that might lead to an underestimation of other causes of the increased risk of premature death.[3,7] Persons with psychiatric comorbid conditions are at a higher risk of dying prematurely of injuries, poisoning, and suicide.[8,9] Yet, our knowledge about premature death in epilepsy is insufficient.[6]

A new systematic classification of mortality in epilepsy was suggested in 2016.[7] Its purpose is to increase awareness of the full spectrum of epilepsy-related mortality and, by more precise estimates of its frequency, to support efforts to prevent it.

With this classification, a systematic review of mortality in persons with epilepsy reported that 60% of all deaths could be classified as epilepsy related.[3] This review did not report frequencies of the different causes of epilepsy-related death. Therefore, we applied the classification[7] to investigate the proportion of epilepsy-related deaths in a nationwide population-based cohort of all Danish citizens 1 to 49 years of age with prevalent epilepsy during 2007 to 2009. Furthermore, we compared premature mortality in persons with and without epilepsy in our cohort.

The aim was to estimate cause-specific and overall epilepsy-related mortality in children and adults <50 years of age.

Methods

Study Design and Population

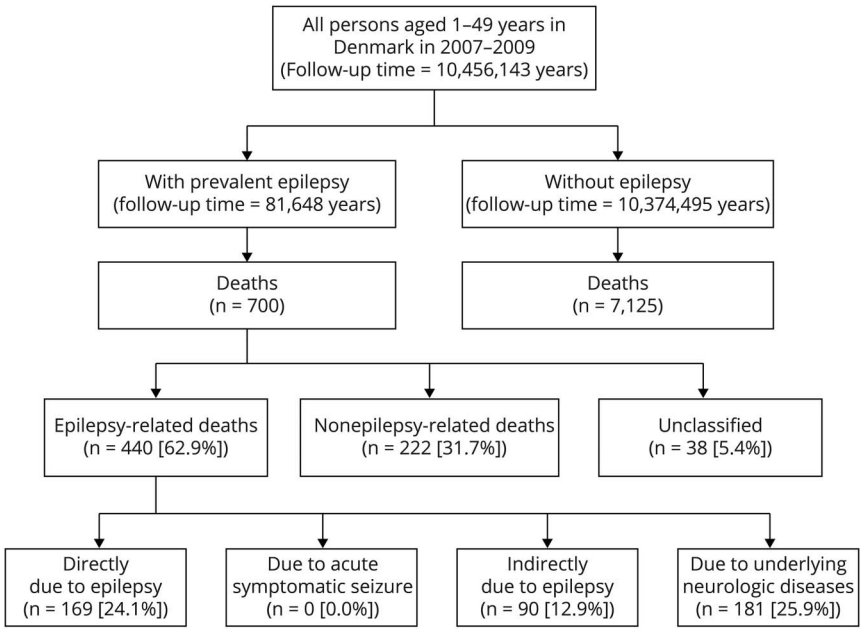
The study was a population-based retrospective cohort study with prevalent epilepsy as the exposure. All Danish citizens >1 and <50 years of age with residence in Denmark during 2007 to 2009 were included in the study population.

In Denmark, all residents are assigned a unique personal civil registration number, which can be linked to national registries at an individual level. For this study, we retrieved individual data from various sources.

The Danish Civil Registry contains personal identification numbers, including dates of migration to and from Denmark, and vital data on all residents in Denmark. These data were used for the identification of all study participants. We retrieved information on all hospitalizations in Denmark since 1977 and all inpatient and outpatient contacts with the secondary health care sector since 1994 from the Danish National Patient Registry. All contacts are registered with ICD-8 codes until 1993 and with ICD-10 codes since 1994 becauseICD-9 was never implemented in Denmark. The Danish National Prescription Registry contains information on all medicine prescriptions to all residents coded according to the Anatomic Therapeutic Chemical (ATC)/defined daily dose system. It is mandatory by law to provide data to the registry, and the data do not depend on manual input. Therefore, the registry is regarded as valid and complete.[10] All information on the study population was retrieved. We used the Danish Cause of Death Registry for information on the primary, contributing, and underlying causes, as well as place of death in all deceased persons during the study period. All causes of death are registered with ICD-8 codes until 1993 and with ICD-10 codes since 1994. In Denmark, it is mandatory by law to complete death certificates. Data from death certificates are transferred to the registry and are validated by the Danish Health Data Authority, so the underlying causes of death are in accordance with the guidelines from the World Health Organization. Furthermore, ≈20% of all death certificates are manually validated; thus, the accuracy of the registry depends mainly on the physicians completing the death certificates. Furthermore, the primary and underlying causes of death are included in all death certificates, and contributing causes can be added. Mode, place, and time of death are registered. Circumstances at death, findings at postmortem examinations, and additional information can be added in a text string. We retrieved all death certificates for all deceased individuals in the study population. Autopsies have to be performed if the external examination cannot establish the mode of death or at the request of physicians or relatives. Information from the autopsy reports, including toxicology examinations, is also added to the death certificate. All available autopsies were collected.

In accordance with the recommendations from the International League Against Epilepsy (ILAE) for epilepsy

Figure 1 Flowchart for All-Cause Mortality Including Epilepsy-Related Death in Persons With Epilepsy 1 to 49 Years of Age During 2007 to 2009



ascertainment in epidemiologic studies,[11] we defined persons with epilepsy as anyone with an epilepsy diagnosis (ICD-10: G40.x; ICD-8: 345.xx [excluding 345.2x, status epilepticus]) in the Danish National Patient Registry and a prescription of any antiseizure medication (ASM) (ATC code: N03xxxx or N05BA09) in the Danish National Prescription Registry. Furthermore, to avoid including persons with resolved epilepsy in the exposure group, we required that persons with prevalent epilepsy had at least 1 encounter due to epilepsy, status epilepticus, or seizure (ICD-10: G40.x, F80.3, G41.x, R25.2, R56.x; ICD-8: 345.xx, 331.29, 780.2x) during the last 10 years before study entry or had a prescription of any ASM (ATC code: N03xxxx or N05BA09) during the last 5 years before study entry. This is in accordance with the ILAE definition for resolved epilepsy.[12]

Other studies have defined persons with epilepsy as anyone with 2 contacts for epilepsy or seizure on 2 separate encounters but without the requirement of ASM use.[13] In a sensitivity analysis, we added the requirement of 1 extra contact due to epilepsy, status epilepticus, or seizure (ICD-10: G40.x, F80.3, G41.x, R25.2, R56.x; ICD-8: 345.xx, 331.29, 780.2x) at a second encounter to our definition of epilepsy.

All study participants were followed up from January 1, 2007, date of 1-year birthday, or date of naturalization as a Danish citizen, whichever came last, and until December 31, 2009, date of death, date of migration from Denmark, or date of 50th birthday, whichever came first. Delayed entry was possible. Persons diagnosed with epilepsy after entering the study had their follow-up time split into before and after exposure. We recorded baseline characteristics as age, sex, and comorbid conditions at entry.

We used the date of the first seizure recorded due to a diagnosis code for epilepsy, status epilepticus, or seizure (ICD-10: G40.x, F80.3, G41.x, R25.2, R56.x; ICD-8: 345.xx, 331.29, 780.2x) as a surrogate for the date of epilepsy onset. The duration of epilepsy was defined as the period from epilepsy onset until study entry.

A Charlson Comorbidity Index was estimated from ICD-8 and ICD-10 diagnosis codes retrieved from the Danish National Patient Registry (eTable 1, links.lww.com/WNL/B661).[14-16]

Three neurologists, 1 neuro-pediatrician, and 2 cardiologists independently evaluated all available information on primary causes of death in the cohort of persons with epilepsy, including SUDEP categorized by the unified SUDEP criteria.[17] A pathologist was consulted on ambiguous cases. In case of disagreement on the cause of death, a decision was made in consensus.

On the basis of the primary causes of death, epilepsy-related mortality was classified as directly due to epilepsy, acute symptomatic seizures, or underlying neurologic disease or indirectly due to epilepsy.[7] Deaths directly due to epilepsy were caused by SUDEP, status epilepticus, drowning, motor vehicle accidents, falls, burns, and other seizure-related accidents. Deaths due to acute symptomatic seizures were death with or without status epilepticus, occurring within 1 week of stroke, traumatic brain injury, anoxic encephalopathy, intracranial surgery, first identification of subdural hematoma,

Table 1 Characteristics of Persons With Epilepsy 1 to 49 Years of Age During 2007 to 2009

	Persons with epilepsy			
	All	Male	Female	*p* Value (male/female)
Population, n (%)	30,437 (0.8)	15,662 (51.5)	14,775 (48.5)	
Follow-up time, mean (SD), PY	81,648, 2.7 (0.7)	41,886, 2.7 (0.7)	39,762, 2.7 (0.7)	0.05
Age at onset of epilepsy, mean (SD), y	17.6 (13.1)	17.6 (13.3)	17.5 (12.8)	0.39
Duration of epilepsy, mean (SD), y	10.3 (8.8)	10.3 (8.8)	10.4 (9.0)	0.09
Children (1–17 y of age), n (%)	7,906 (26.0)	4,168 (26.6)	3,738 (25.3)	
Charlson Comorbidity Index, n (%)				0.01
0	23,397 (76.9)	11,926 (76.2)	11,471 (77.6)	
1	3,244 (10.7)	1,709 (10.9)	1,535 (10.4)	
2	2,558 (8.4)	1,354 (8.7)	1,204 (8.2)	
>2	1,238 (4.1)	673 (4.3)	565 (3.8)	
Deceased during 2007–2009, n (%)	700 (2.3)	427 (2.7)	273 (1.9)	<0.0001
Age at death, mean (SD), y	36.3 (12.3)	36.2 (12.1)	36.6 (12.6)	0.64
Witnessed, n (%)	73 (10.4)	44 (10.3)	29 (10.6)	0.11
Cardiopulmonary resuscitation, n (%)	66 (9.4)	34 (8.0)	32 (11.7)	0.18
Autopsy, n (%)	135 (19.3)	93 (21.8)	42 (15.4)	0.04
Toxicology performed, n (%)	101 (14.4)	72 (16.9)	29 (10.6)	0.03
History of alcohol misuse, n (%)	158 (22.6)	115 (26.9)	43 (15.8)	0.0006
History of drug misuse, n (%)	81 (11.6)	60 (14.1)	21 (7.7)	0.01

Abbreviation: PY = person-years.

CNS infection, or an active phase of multiple sclerosis and other autoimmune disorders. Deaths indirectly due to epilepsy included aspiration pneumonia, suicide, and cardiovascular disease that might have been exacerbated or caused by ASMs. Deaths due to underlying neurologic disease were caused by brain tumors, stroke, metabolic, genetic, or neurodegenerative diseases.[7] To meet the criteria for deaths due to acute symptomatic seizures, the included underlying conditions should be present, and the cause of death should be a seizure and not the underlying condition.

SUDEP was defined by the unified criteria as sudden, unexpected, nontraumatic, and nondrowning death, excluding status epilepticus, and no identification of a cause of death at the postmortem examination.[17] We categorized SUDEP as definite when all criteria were fulfilled, definite plus when all criteria were fulfilled but another contributing condition was also identified, probable when all criteria were fulfilled but autopsy was not performed, possible when a competing cause of death was present, or fatal near-SUDEP when the decedent survived a potential SUDEP for >1 hour but then died while in intensive care.[17] For the evaluation of epilepsy-related deaths, we included the total number of SUDEP cases by pooling all subgroups.

The ascertainment of aspiration pneumonia and other causes and modes of death such as suicide was based on the evaluation of all available information, not solely on postmortem examinations. Cases with incomplete information were deemed unclassifiable.

All underlying causes of death in the entire Danish population 1 to 49 years of age during 2007 to 2009 were categorized as shown in eTable 2, links.lww.com/WNL/B661,[18] and they were compared between persons with and without epilepsy. This comparison was based on ICD-8 and ICD-10 codes in the Danish Cause of Death Registry. In this comparison we categorized deaths as connected to either suicide or drug overdose. Persons 1 to 17 years of age were referred to as children, and persons 18 to 49 years of age were referred to as younger adults.

Statistics

Mortality rates with 95% confidence intervals (CI) for all-cause mortality and for specific causes of death were estimated with a Poisson regression model. We used hazard ratios with 95% CIs for the comparison of causes or modes of death, estimated with a Cox regression model. Both the Poisson model and the Cox regression model were multivariable

Table 2 All-Cause Mortality Rates for Persons With Epilepsy 1 to 49 Years of Age During 2007 to 2009, Stratified on Sex

	All		Male		Female				
	Cases/ PY	Incidences/ 1,000 PY (95% CI)	Cases/ PY	Incidences/ 1,000 PY (95% CI)	Cases/ PY	Incidences/ 1,000 PY (95% CI)	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)	Adjusted HR[d] (95% CI)
All	700/ 81,648	8.57 (7.96–9.23)	427/ 41,886	10.19 (9.27–11.21	273/ 39,762	6.87 (6.10–7.73)	1.48 (1.27–1.73)[a]	1.48 (1.27–1.72)[a]	1.43 (1.23–1.66)[a]
1–17 y	76/ 18,728	4.06 (3.24–5.08)	45/ 9,976	4.51 (3.37–6.04)	31/ 8,752	3.54 (2.49–5.04)	1.28 (0.81–2.02), $p = 0.29$	1.26 (0.80–2.00), $p = 0.32$	1.17 (0.74–1.85), $p = 0.50$
18–49 y	624/ 62,920	9.92 (9.17–10.73)	382/ 31,910	11.97 (10.83–13.23)	242/ 31,010	7.80 (6.88–8.85)	1.53 (1.31–1.80)[a]	1.49 (1.27–1.76)[a]	1.46 (1.24–1.71)[a]

Abbreviations: CI = confidence interval; HR = hazard ratio; PY = person-years.
[a] $p < 0.0001$.
[b] Between male and female.
[c] Between male and female, adjusted for age and sex.
[d] Between male and female, adjusted for age, sex, and comorbid conditions.

regression models with death as outcome and sex, age at entry, and Charlson Comorbidity Index as predicting variables.

Differences between groups were compared with a Fisher exact test for categorical variables and a 2-sided *t* test for continuous variables as appropriate.

A value of $p = 0.05$ defined the level of significance. Due to the descriptive study design, no adjustments for multiple comparisons were made.

All statistics were performed with SAS Enterprise Guide (version 7.1) (SAS Institute Inc, Cary, NC) and RStudio (version 1.1.463) (RStudio, Inc, Boston, MA) with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, 2020).

Standard Protocol Approvals, Registrations, and Patient Consents

The study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (P-2020-341 and P-2020-344). Individual informed consent was not needed.

Data Availability

Anonymized data will be shared by request from qualified investigators.

Results

During 2007 to 2009, the mean population of Denmark was 5.5 million people. Within this population, we identified a total of 3,838,293 individuals 1 to 49 years of age (50.9% male) followed up for 10,456,143 person-years with 7,825 deaths (0.2% of the population) at the end of the follow-up period. Of these, 30,437 individuals had prevalent epilepsy (51.5% male) and were followed up for 81,648 person-years, equaling a period prevalence of epilepsy of 0.8% in the general population. A total of 700 deaths in persons with epilepsy 1 to 49 years of age were identified (2.3% of all persons with epilepsy) (Figure 1). The characteristics of persons with epilepsy are shown in Table 1.

Children 1 to 17 years of age accounted for 76 deaths, of which 59.2% occurred in male individuals. In younger adults 18 to 49 years of age, 624 deaths were registered, 61.2% in male individuals.

Mortality Rates

The all-cause mortality rate in persons with epilepsy 1 to 49 years was estimated at 8.57 per 1,000 person-years (95% CI 7.96–9.23) (Table 2).

After adjustment for sex and Charlson Comorbidity Index, younger adults had a 2.7-fold higher mortality rate compared with children (adjusted hazard ratio 2.73 [95% CI 2.15–3.47], $p < 0.0001$) (eTable 3, links.lww.com/WNL/B661).

Sex differences in mortality rates were statistically significant in adults but not in children (Table 2).

In persons with epilepsy, the mortality rate decreased from 5.50 per 1,000 person-years (95% CI 3.93–7.70) in the first decade to 3.47 per 1,000 person-years (95% CI 2.67–4.52) in the second decade. From the second decade and onward, the mortality rate increased for each decade toward a maximum of 16.48 per 1,000 person-years (95% CI 14.91–18.24) in persons 40 to 49 years of age. In persons without epilepsy, the mortality rate increased throughout all decades from 0.09 per 1,000 person-years (95% CI 0.08–0.11) in children 1 to 9 years of age to 1.79 per 1,000 person-years (95% CI 1.73–1.84) in adults 40 to 49 years of age.

Causes of Death

A total of 135 decedents were autopsied (19.3%). The autopsy rate was higher in non–epilepsy-related deaths (27.5% vs 16.6%, $p < 0.0001$). In children, the autopsy rate was 7.9%, while it was 20.7% in younger adults ($p = 0.01$).

The 3 most frequent primary causes of death in persons with epilepsy were brain tumor (21.3%), SUDEP (19.3%), and

Table 3 Epilepsy-Related Deaths in All Persons With Epilepsy and in Adults, Children, Male Individuals, and Female Individuals, Including the 3 Most Frequent Causes of Death

Cause of death	Frequency	Percentage of all deaths	Percentage of all epilepsy-related deaths
All			
Epilepsy-related deaths	440	62.9	100.0
Brain tumor	149	21.3	33.9
SUDEP	135	19.3	30.7
Aspiration pneumonia	72	10.3	16.4
Children			
Epilepsy-related deaths	58	76.3	100.0
Aspiration pneumonia	24	31.6	41.4
SUDEP	11	14.5	19.0
Metabolic, genetic, or neurodegenerative diseases	9	11.8	15.5
Adults			
Epilepsy-related deaths	382	61.2	100.0
Brain tumor	142	22.8	37.2
SUDEP	124	19.9	32.5
Aspiration pneumonia	48	7.7	12.6
Male individuals			
Epilepsy-related deaths	265	62.1	100.0
SUDEP	84	19.7	31.7
Brain tumor	82	19.2	20.9
Aspiration pneumonia	43	10.1	16.2
Female individuals			
Epilepsy-related deaths	175	64.1	100.0
Brain tumor	67	24.5	38.3
SUDEP	51	18.7	29.1
Aspiration pneumonia	29	10.6	16.6

Abbreviation: SUDEP = sudden unexplained death in epilepsy.

aspiration pneumonia (10.3%) (Table 3). These 3 causes accounted for 80.9% of all epilepsy-related deaths.

In comparison, 4.6% of all decedents died of alcohol-related causes, 3.6% of cardiovascular diseases, 2.6% of causes related to suicide, and 0.9% of status epilepticus. Deaths related to accidents accounted for 7.6% of all deaths. Accidents were directly related to seizures in 52.8% of these deaths (28 of 53 deaths related to accidents). In addition to aspiration pneumonia, 2.3% of all deaths were caused by other types of pneumonia.

Compared with the underlying causes of death registered in the Danish Cause of Death Register, our re-evaluation of all deaths in persons with epilepsy revealed more deaths due to primary brain cancer (105 cases vs 100 cases), status epilepticus (6 cases vs 5 cases), suicide (18 cases vs 12 cases), and pneumonia (88 cases vs 15 cases) but fewer deaths related to accidents (53 cases vs 66 cases).

When the primary causes of death were classified as suggested by Devinsky et al.,[7] 440 (62.9%) of all deaths were epilepsy related (Figure 2). We did not find any statistically significant sex differences.

Within the subcategories of epilepsy-related death, most cases either were due to an underlying neurologic disease (41.1%) or were directly related to epilepsy (38.4%).

Among deaths directly related to epilepsy, SUDEP was the leading cause. Male individuals accounted for most seizure-related accidents (14 of 18), and all 4 deaths related to drowning occurred in male individuals, although the sex differences were not statistically significant.

Aspiration pneumonia was the leading cause among deaths indirectly related to epilepsy (80%). A majority of suicide cases (72.2%) were men. No children died by suicide or died of poisoning with ASM.

Regarding deaths due to underlying neurologic diseases, brain tumor was the leading cause (82.3%).

The frequency of epilepsy-related deaths in children and younger adults is summarized in Table 3.

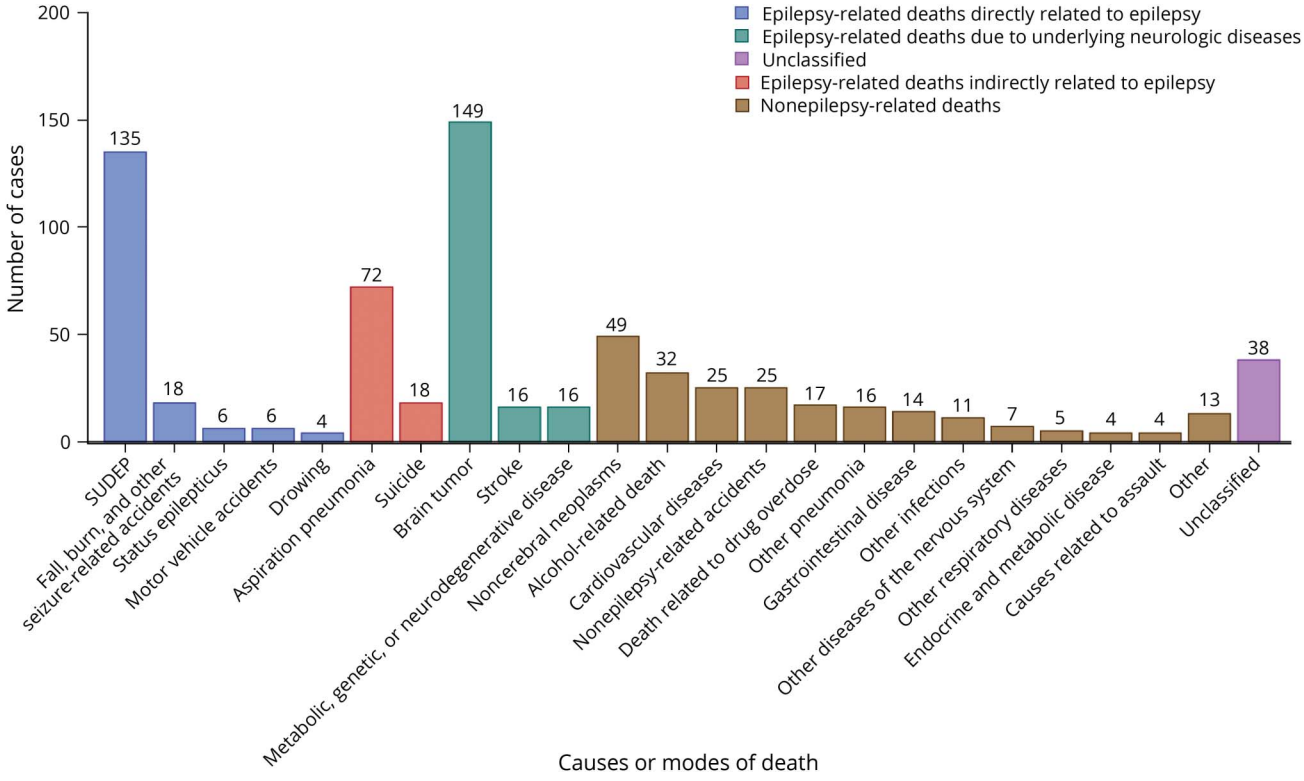
In a sensitivity analysis in which we added the requirement of an extra encounter for epilepsy, status epilepticus, or seizure to our definition of epilepsy, the prevalence of epilepsy decreased to 0.7%. Within this population, 2.3% died during the study period, and 65.6% of these deaths were epilepsy related.

Risk of Death

The risk of death in persons with epilepsy 1 to 49 years of age, adjusted for age, sex, and comorbid conditions, was increased nearly 4-fold compared with the background population (adjusted mortality hazard ratio between persons with and without epilepsy 3.95 [95% CI 3.64–4.27], $p < 0.0001$). The absolute risk difference was 8 extra deaths per 1,000 person-years (Table 4).

In terms of specific causes of death, persons with epilepsy had an increased mortality from all causes and modes of death compared with persons without epilepsy (Table 5). After

Figure 2 Causes and Modes of Death in Persons With Epilepsy 1 to 49 Years of Age During 2007 to 2009 Grouped Into Epilepsy-Related Death and Non–Epilepsy-Related Death



SUDEP = sudden unexplained death in epilepsy.

adjustment for age, sex, and Charlson Comorbidity Index, the elevated risk persisted for all categories, with the exclusion of other respiratory diseases and unclassified causes. The adjusted hazard ratios between persons with and without epilepsy ranged from 1.22 (95% CI 1.01–1.50, $p = 0.04$) for noncerebral neoplasms to 2.10 (95% CI 1.18–3.73, $p = 0.01$) for causes related to suicide, 2.90 (95% CI 1.63–5.14, $p = 0.0002$) for gastrointestinal diseases, 24.55 (95% CI 18.41–32.74, $p < 0.0001$) for brain tumor, 50.21 (95% CI 39.26–64.23, $p < 0.0001$) for other neurologic diseases, and 181.40 (95% CI 31.10–1,058.17, $p < 0.0001$) for status epilepticus (Table 5).

Discussion

In this nationwide population-based study applying a newly proposed classification of epilepsy-related mortality[7] to a cohort of children and adults <50 years of age, we demonstrated that 63% of all premature deaths were epilepsy related. Furthermore, we found that the risk of death in persons with epilepsy was increased compared with the background population during the study period.

Most epilepsy-related deaths were related either to an underlying neurologic disease or directly to epilepsy. The risk of death directly related to epilepsy was nearly 2-fold higher than the risk indirectly related to epilepsy. In children, however, most deaths were indirectly related to epilepsy. We found no deaths of acute symptomatic causes because the study population consisted only of persons already diagnosed with epilepsy.

The proportion of epilepsy-related deaths in our cohort is comparable to the systematic review of all-cause mortality from 2019, which reported 60% of all deaths as epilepsy related.[3] This study reported that the highest risk of death in persons with epilepsy was caused by brain tumors, but the frequency of different causes or modes of death was not reported. We found that brain tumors were the most frequent cause of premature death in children and younger adults (21.3% of all deaths), but when we included individual data from the Danish Cause of Death Registry, death certificates, and autopsy reports, the proportion of SUDEP was almost as high (19.3%). In agreement with other studies,[19] we found that SUDEP was the leading cause of unexpected death. SUDEP accounted for nearly one-third of all epilepsy-related deaths and for 8 of 10 deaths directly related to seizures. Regarding SUDEP, we used the existing unified SUDEP definition[17] because no specific definition was described in the classification of epilepsy-related death.[7] Applying the new classification therefore had no effect on the SUDEP assessment in the population. However, using the classification

Table 4 All-Cause Mortality for Persons With and Without Epilepsy

	Persons with epilepsy		Persons without epilepsy				
	Cases/PY	Incidence/1,000 PY (95% CI)	Cases/PY	Incidence/1,000 PY (95% CI)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Adjusted HR[c] (95% CI)
All-cause mortality							
All	700/81,648	8.57 (7.96–9.23)	7,125/ 10,374,495	0.69 (0.67–0.70)	12.48 (11.54–13.48)[a]	10.77 (9.97–11.64)[a]	3.95 (3.64–4.27[a]
1–17 y	76/18,728	4.06 (3.24–5.08)	369/ 3,438,947	0.11 (0.10–0.12)	37.42 (29.23–47.91)[a]	35.71 (27.81–45.85)[a]	5.56 (4.17–7.41)[a]
18–49 y	624/62,920	9.92 (9.17–10.73)	6,756/ 6,935,548	0.97 (0.95–1.00)	10.18 (9.38–11.05)[a]	9.94 (9.15–10.79)[a]	3.75 (3.45–4.07)[a]

Abbreviations: CI = confidence interval; HR = hazard ratio; PY = person-years.
[a] $p < 0.0001$.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, and Charlson Comorbidity Index.

made it possible to compare the burden of SUDEP with other epilepsy-related deaths.

Our re-evaluation of the circumstances of death, including postmortem examinations when available, revealed more cases of death from pneumonia than reported as an underlying cause. Many of these cases were in persons with metabolic disorder or cerebral palsy, and these conditions were stated as the underlying cause of death. This distinction would not be possible if we used register-based data only. Aspiration pneumonia was most frequent in patients with severe comorbid conditions. However, only 5.6% of deaths from aspiration pneumonia were verified by autopsy. The remaining cases were based on other available information, including the described circumstances at death.

The new classification was particularly useful in the assessment of unnatural deaths in epilepsy by categorizing these as either related to seizures or not. For instance, in some motor vehicle accidents, the decedent was a passenger, thereby not dying due to a seizure-related accident. Again, this distinction would not be possible without combining data from different sources.

The low frequency of deaths related to drowning was in line with a previous study of mortality in Danish children with epilepsy.[20] One explanation could be that children are recommended to swim under observation. Similarly, we found a low frequency of death due to stroke compared to brain tumors. This might be explained by the low frequency and mortality of stroke found in the included age groups[21] and that seizures might be more frequently related to brain tumors than to stroke.[22,23]

In studies of mortality based solely on the primary and contributing causes of death, the leading causes of death in persons with epilepsy have been reported as cancer, cerebrovascular diseases, pneumonia, and ischemic heart disease.[24] In our study, with additional data sources, cancer, SUDEP, and pneumonia were the 3 most frequent causes of death.

Not all epilepsy-related deaths are preventable, while some non–epilepsy-related deaths are. This could be emphasized in future updates of the classification. Likewise, the inclusion of death resulting from underlying neurologic disease such as brain tumors in the classification as epilepsy-related deaths can be debated. The included diseases are strongly related to epilepsy, and the subcategory of deaths due to underlying neurologic diseases was the most frequent in children and younger adults with epilepsy. Excluding death from underlying neurologic disease would lower the burden of epilepsy-related death to 37.0% of all deaths in the population. However, using the 4 subcategories of epilepsy-related death makes it possible to compare death directly related to seizures with other causes of death.

The increased mortality in our cohort is in agreement with other reports of all-cause mortality in children and younger adults with epilepsy.[5,25,26] The risk of death in persons with epilepsy <50 years of age was nearly increased 11-fold when adjusted for age and sex. For comparison, a Danish study of all-cause mortality in persons 1 to 49 years of age with diabetes mellitus found an age- and sex-adjusted 4-fold increased risk of death compared with the background population.[27]

When additionally adjusted for comorbid conditions, the risk of death in persons with epilepsy was increased 4-fold, indicating that some of the increased mortality in epilepsy might be explained by the overall burden of comorbid conditions in these persons.

In children with epilepsy, we estimated the highest risk of death during the first decade, then decreasing risk in children and teenagers 10 to 19 years of age. This pattern was not observed in children without epilepsy, in whom mortality

Table 5 Underlying Causes and Modes of Death in Persons With and Without Epilepsy

	Persons with epilepsy	Persons without epilepsy			
Cause of death	Incidence/1,000 PY (95% CI)	Incidence/1,000 PY (95% CI)	Crude HR (95% CI), *p* value	Adjusted[b] HR (95% CI), *p* value	Adjusted[c] HR (95% CI), *p* value
Other infections	0.10 (0.05–0.20)	0.01 (0.01–0.01)	8.27 (4.04–16.90)[a]	7.29 (3.56–14.90)[a]	2.39 (1.16–4.95), $p = 0.02$
Primary cerebral neoplasm	1.23 (1.01–1.49)	0.01 (0.01–0.01)	121.80 (92.60–160.30)[a]	107.05 (81.32–140.93)[a]	24.55 (18.41–32.74)[a]
Noncerebral neoplasms	1.10 (0.90–1.36)	0.16 (0.15–0.17)	6.87 (5.56–8.49)[a]	5.83 (4.72–7.21)[a]	1.22 (1.01–1.50), $p = 0.04$)
Endocrine and metabolic disorders	0.32 (0.22–0.47)	0.02 (0.02–0.03)	13.07 (8.73–19.57)[a]	11.27 (7.53–16.87)[a]	3.30 (2.19–4.87)[a]
Mental and behavioral disorders	0.40 (0.28–0.55)	0.01 (0.01–0.01)	38.05 (25.64–56.48)[a]	32.80 (22.10–48.70)[a]	21.70 (14.28–32.97)[a]
Status epilepticus	0.06 (0.03–0.15)	0.00 (0.00–0.00)	317.60 (61.63–1,637.00)[a]	315.91 (60.72–1,643.53)[a]	181.40 (31.10–1,058.17)[a]
Other diseases in the nervous system	1.63 (1.37–1.93)	0.02 (0.01–0.02)	98.81 (78.78–123.90)[a]	87.88 (70.03–110.28)[a]	50.21 (39.26–64.23)[a]
Cardiovascular diseases	0.71 (0.55–0.92)	0.09 (0.08–0.10)	7.90 (6.06–10.30)[a]	6.64 (5.09–8.66)[a]	3.05 (2.33–3.99)[a]
Pneumonia	0.18 (0.11–0.31)	0.01 (0.00–0.01)	35.24 (19.89–62.45)[a]	30.90 (17.43–54.79)[a]	14.22 (7.74–26.14)[a]
Other respiratory diseases	0.06 (0.03–0.15)	0.01 (0.01–0.01)	5.26 (2.15–12.86), $p = 0.0003$	4.52 (1.85–11.06), $p = 0.001$	1.84 (0.74–4.54), $p = 0.19$
Gastrointestinal diseases	0.16 (0.09–0.27)	0.02 (0.01–0.02)	10.00 (5.69–17.59)[a]	8.36 (4.75–14.70)[a]	2.90 (1.63–5.14), $p = 0.0002$
Renal and genitourinary disorders	0.07 (0.03–0.16)	0.00 (0.00–0.00)	23.88 (9.98–57.10)[a]	20.27 (8.47–48.48)[a]	5.50 (2.27–13.34), $p = 0.0002$
Congenital disorders	0.33 (0.23–0.48)	0.01 (0.01–0.01)	41.23 (26.71–63.65)[a]	42.86 (27.69–66.35)[a]	12.30 (7.60–19.89)[a]
Accident-related deaths	0.81 (0.64–1.03)	0.14 (0.13–0.15)	5.72 (4.47–7.31)[a]	5.22(4.08–6.68)[a]	3.81 (2.96–4.90)[a]
Alcohol-related death	0.75 (0.58–0.96)	0.07 (0.06–0.08)	10.77 (8.30–13.99)[a]	8.81 (6.79–11.45)[a]	2.91 (2.23–3.80)[a]
Causes related to suicide	0.15 (0.08–0.26)	0.06 (0.05–0.06)	2.69 (1.52–4.76), $p = 0.0007$	2.35 (1.33–4.17), $p = 0.003$	2.10 (1.18–3.73), $p = 0.01$
Assaults	0.06 (0.03–0.15)	0.01 (0.01–0.01)	7.48 (3.03–18.43)[a]	7.02 (2.85–17.32)[a]	5.39 (2.14–13.57), $p = 0.0003$
Drug overdose	0.12 (0.07–0.23)	0.02 (0.02–0.02)	6.93 (3.67–13.10)[a]	6.01 (3.18–11.35)[a]	3.61 (1.89–6.90)[a]
Unclassified	0.05 (0.02–0.13)	0.02 (0.02–0.02)	2.84 (1.05–7.65), $p = 0.04$	2.41 (0.89–6.49), $p = 0.08$	1.95 (0.72–5.30), $p = 0.19$

Abbreviations: CI = confidence interval; HR = hazard ratio; PY = person-years.
[a] $p < 0.0001$.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, and Charlson Comorbidity Index.

increased throughout all age groups. The high risk of death in children with epilepsy during the first decade could be explained by several severe epileptic syndromes.[28,29] Aspiration pneumonia was the leading cause of epilepsy-related death in children, indicating a high proportion of severe disease in this group.

In agreement with other studies, we found that children and younger adults with epilepsy had an increased risk of death resulting from many underlying causes compared with the background population.[24,30-34] This elevated risk persisted when adjusted for age, sex, and comorbid conditions. This suggests that epilepsy itself is associated with an increased risk of death from various causes.

Our estimate regarding death from pneumonia was in line with other studies of all-cause mortality.[24,25,30,31,33,34] Many of these deaths occurred during a worsening of the patient's overall condition but with pneumonia as the primary cause of death. All these deaths were expected.

Regarding suicide, our re-evaluation of the available information revealed 33.3% extra cases. This is in accordance with other studies reporting that deaths related to suicide are frequently missed in registries when only diagnosis codes are used for the ascertainment.[35] A validation study of the Danish Cause of Death Registry reported that 90% of the registered suicides were confirmed, with the highest uncertainty for poisoning suicides.[36] However, not all suicides were classified as such in the registry. For the comparison of causes and modes of death in persons with epilepsy, we used the suicide cases found by our evaluation of all death. However, we were not able to evaluate all deaths in persons without epilepsy. Therefore, we decided to categorize deaths as connected to either suicide or drug overdose because this seemed to be the best way to capture deaths connected to suicide in persons with epilepsy. If deaths connected to drug overdose were added to the category of suicide, half of all suicide cases in persons with epilepsy would have been incorrect. Using this definition, we found a 2-fold increased risk in persons with epilepsy. This was comparable to previous reports including all age groups in which the standardized mortality ratios for suicide range between 0.9 and 16.0.[1] However, our study supports the notion that suicide is not the main contributor to the overall increased risk of death in the young.[5]

The risk of assaults leading to death was 5 time higher in persons with epilepsy. These assaults seemed to be random acts of violence and did not happen in relation to a seizure.

Our study included the entire Danish population 1 to 49 years of age during 2007 to 2009 and thus all prevalent epilepsy cases in this population. The comprehensive evaluation of all deaths in the population made it possible to assess the burden of epilepsy-related deaths in children and younger persons with epilepsy, who have a higher risk of death compared with older persons.[3,6] Children <1 year of age are often characterized with a specific pattern of premature death.[37] Therefore, we excluded this separate age group from the cohort.

Because our data were register based, we could not perform analyses stratified by seizure frequency or subgroups of epilepsy.[38] Furthermore, the register-based data might lead to potential misclassification because the positive predictive value of an epilepsy diagnosis in the Danish National Patient Registry is reported to be 81%.[38] We tried to address this issue by adding the requirement of ASM use to the definition of epilepsy, as suggested by the ILAE.[11] In our definition of epilepsy, potential misclassification would still be possible because a person misdiagnosed with epilepsy and with a prescription of ASM for another condition, for example, migraine prophylaxis, would meet the inclusion criteria. However, in the sensitivity analysis in which >1 encounter due to epilepsy or recurrent seizures was required together with ASM use, the prevalence of epilepsy was only slightly decreased, while the proportions of deaths, including epilepsy-related deaths, remained comparable.

The low autopsy rate was another limitation. The uncertainty of the causes of death was not related only to the proportion of unclassified cases (5.4%). The low autopsy rate could also overestimate other causes of death such as SUDEP because this category included nonautopsied cases. The autopsy rate was especially low in children. This stresses the importance of postmortem examination in all age groups to increase the knowledge of all-cause mortality in search for preventive strategies.

Our study indicates that using only register-based data for assessing epilepsy-related deaths may be associated with several pitfalls. Without additional information on the circumstances of death, cases of SUDEP, aspiration pneumonia, and seizure-related accidents and complications will be underreported or misreported.

This nationwide study demonstrated that the newly proposed classification of epilepsy-related mortality was useful for the categorization of the cause of death in an unselected cohort of children and adults <50 years of age. The classification especially helped in classifying unnatural causes of death as related to epilepsy or not and made it possible to distinguish between different types of epilepsy-related death, for instance, deaths directly or indirectly related to seizures.

Applying the new classification showed that >6 of 10 deaths were related to epilepsy and thus in some cases were potentially preventable. Furthermore, we found that persons with epilepsy had a nearly 4-fold increased mortality compared with the background population and that the risk of death was increased for most causes or modes of death.

This underlines the importance of good seizure control and patient empowerment in the prevention of premature death.

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References

1. Watila MM, Balarabe SA, Ojo O, Keezer MR, Sander JW. Overall and cause-specific premature mortality in epilepsy: a systematic review. *Epilepsy Behav.* 2018;87: 213-225.
2. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019; 18(4):357-375.
3. Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM. Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews. *Epilepsy Res.* 2019;157:106192.
4. DeGiorgio CM, Curtis A, Carapetian A, Hovsepian D, Krishnadasan A, Markovic D. Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. *BMJ Open.* 2020;10(8):e035767.
5. Christensen J, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term mortality in children and young adults with epilepsy: a population-based cohort study. *Epilepsy Res.* 2015;114:81-88.
6. Thurman DJ, Logroscino G, Beghi E, et al. 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. *Epilepsia.* 2017;58(1): 17-26.
7. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. *Neurology.* 2016;86(8):779-786.
8. Gorton HC, Webb RT, Carr MJ, DelPozo-Banos M, John A, Ashcroft DM. Risk of unnatural mortality in people with epilepsy. *JAMA Neurol.* 2018;75(8): 929-938.
9. Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet.* 2013;382(9905):1646-1654.
10. The Danish Health Data Authority. The Danish National Prescription Registry. 29-08-2021; 2021. Updated September 13, 2016. Accessed August 29, 2021. esundhed.dk/Dokumentation/DocumentationExtended?id=14.
11. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia.* 2011;52(suppl 7):2-26.
12. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia.* 2014;55(4):475-482.
13. Kalilani L, Faught E, Kim H, et al. Assessment and effect of a gap between new-onset epilepsy diagnosis and treatment in the US. *Neurology.* 2019;92(19): e2197-e2208.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
15. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson comorbidity index: ICD-9 update and ICD-10 translation. *Am Health Drug Benefits.* 2019;12(4):188-197.
16. Raedkjaer M, Maretty-Kongstad K, Baad-Hansen T, et al. The impact of comorbidity on mortality in Danish sarcoma patients from 2000-2013: a nationwide population-based multicentre study. *PLoS One.* 2018;13(6):e0198933.
17. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia.* 2012;53(2):227-233.
18. Erlangsen A, Andersen PK, Toender A, Laursen TM, Nordentoft M, Canudas-Romo V. Cause-specific life-years lost in people with mental disorders: a nationwide, register-based cohort study. *Lancet Psychiatry.* 2017;4(12):937-945.
19. Karlovich E, Devinsky O, Brandsoy M, Friedman D. SUDEP among young adults in the San Diego County medical examiner office. *Epilepsia.* 2020;61(3):e17-e22.
20. Grønborg S, Uldall P. Mortality and causes of death in children referred to a tertiary epilepsy center. *Eur J Paediatr Neurol.* 2014;18(1):66-71.
21. Yafasova A, Fosbøl EL, Christiansen MN, et al. Time trends in incidence, comorbidity, and mortality of ischemic stroke in Denmark (1996-2016). *Neurology.* 2020;95(17): e2343-e2353.
22. Rasmussen BK, Hansen S, Laursen RJ, et al. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the Danish neuro-oncology registry. *J Neurooncol.* 2017;135(3):571-579.
23. Zhao Y, Li X, Zhang K, Tong T, Cui R. The progress of epilepsy after stroke. *Curr Neuropharmacol.* 2018;16(1):71-78.
24. Neligan A, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. *Brain.* 2011;134(pt 2): 388-395.
25. Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County, MN. *Epilepsia.* 2012;53(12):2164-2171.
26. Holst AG, Winkel BG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia.* 2013;54(9): 1613-1620.
27. Svane J, Lynge TH, Pedersen-Bjergaard U, et al. Cause-specific mortality in children and young adults with diabetes mellitus: a Danish nationwide cohort study. *Eur J Prev Cardiol.* 2019;28(2):159-165.
28. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. *Epilepsy Res.* 2016;128:43-47.
29. Bayat A, Kløvgaard M, Johannesen KM, et al. Deciphering the premature mortality in PIGA-CDG: an untold story. *Epilepsy Res.* 2021;170:106530.
30. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis

of a long-term, prospective, population-based cohort. *Ann Neurol.* 2001;49(3):336-344.
31. Morgan CL, Kerr MP. Epilepsy and mortality: a record linkage study in a U.K. population. *Epilepsia.* 2002;43(10):1251-1255.
32. Lindsten H, Nyström L, Forsgren L. Mortality risk in an adult cohort with a newly diagnosed unprovoked epileptic seizure: a population-based study. *Epilepsia.* 2000;41(11):1469-1473.
33. Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. Mortality from epilepsy: results from a prospective population-based study. *Lancet.* 1994;344(8927):918-921.
34. Ding D, Wang W, Wu J, et al. Premature mortality risk in people with convulsive epilepsy: long follow-up of a cohort in rural China. *Epilepsia.* 2013;54(3):512-517.
35. Thomas KH, Davies N, Metcalfe C, Windmeijer F, Martin RM, Gunnell D. Validation of suicide and self-harm records in the clinical practice research datalink. *Br J Clin Pharmacol.* 2013;76(1):145-157.
36. Tøllefsen IM, Helweg-Larsen K, Thiblin I, et al. Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia. *BMJ Open.* 2015;5(11):e009120.
37. Winkel BG, Holst AG, Theilade J, et al. Sudden unexpected death in infancy in Denmark. *Scand Cardiovasc J.* 2011;45(1):14-20.
38. Christensen J, Vestergaard M, Olsen J, Sidenius P. Validation of epilepsy diagnoses in the Danish national hospital register. *Epilepsy Res.* 2007;75(2-3):162-170.