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CHAPTER 6**CAUSE OF DEATH AND PREDICTORS OF MORTALITY IN A COMMUNITY-BASED COHORT OF PEOPLE WITH EPILEPSY****Mark R. Keezer^{1,2}, Gail S. Bell^{1,2}, Aidan Neligan³, Jan Novy⁴, Josemir W. Sander^{1,2,5}**

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ABSTRACT

Objective: The risk of premature mortality is increased in people with epilepsy. The reasons for this and how it may relate to epilepsy etiology remain unclear.

Methods: The National General Practice Study of Epilepsy is a prospective, community-based cohort that includes 558 people with recurrent unprovoked seizures of whom 34% died during almost 25 years of follow-up. We assessed the underlying and immediate causes of death and their relationship to epilepsy etiology. Psychiatric and somatic comorbidities of epilepsy as predictors of mortality were scrutinized using adjusted Cox proportional hazards models.

Results: The 3 most common underlying causes of death were noncerebral neoplasm, cardiovascular, and cerebrovascular disease, accounting for 59% (111/189) of deaths, while epilepsy-related causes (e.g., sudden unexplained death in epilepsy) accounted for 3% (6/189) of deaths. In 23% (43/189) of individuals, the underlying cause of death was directly related to the epilepsy etiology; this was significantly more likely if death occurred within 2 years of the index seizure (percent ratio 4.28 [95% confidence interval 2.63–6.97]). Specific comorbidities independently associated with increased risk of mortality were neoplasms (primary cerebral and noncerebral neoplasm), certain neurologic diseases, and substance abuse.

Conclusions: Comorbid diseases are important causes of death, as well as predictors of premature mortality in epilepsy. There is an especially strong relationship between cause of death and epilepsy etiology in the first 2 years after the index seizure. Addressing these issues may help stem the tide of premature mortality in epilepsy.

INTRODUCTION

Recent work has highlighted that people with epilepsy have premature mortality relative to the general population. This has been consistently shown in high-income countries such as the United Kingdom,¹ United States,² Sweden,³ and Iceland,⁴ as well as low- to middle-income countries such as Bolivia,⁵ India,⁶ and China.⁷ The reasons for this are not apparent and warrant further investigation.

Prior studies have described the distribution of causes of death (COD) in those with epilepsy but few have distinguished between underlying and immediate causes.⁷⁻¹³ There is a paucity of data examining the relationship between epilepsy etiology and COD.^{14, 15} There have been attempts to describe predictors of premature mortality, including nonadherence to antiepileptic drugs, psychiatric disorders, cognitive impairment, and age,^{11, 16, 17} but there have been no comprehensive assessments of the role of the full spectrum of somatic and psychiatric comorbidities in predicting mortality in an epilepsy cohort.

We describe the underlying and immediate CODs seen in a large community-based prospective cohort of people with epilepsy with almost 25 years of follow-up and inquire into the relationship between underlying COD and epilepsy etiology as well as examine for predictors of mortality, with a particular emphasis on somatic and psychiatric comorbidities.

METHODS

The National General Practice Study of Epilepsy (NGPSE) is a longitudinal cohort study of people with incident epileptic seizures, the methods of which have been described previously.^{1, 18} Participants were initially identified between June 1984 and October 1987 by 275 participating general practitioners (GPs) from across the United Kingdom who were asked to report any person of any age with newly suspected epileptic seizures. A diagnostic panel reviewed all potential participants and identified those with definite or probable epileptic seizures. Of the initial 1,195 people registered, 792 (66.3%) had had epileptic seizures. The remaining individuals were diagnosed with febrile seizures ($n = 220$), previously diagnosed epilepsy or neonatal seizures ($n = 104$), or no clear history of epileptic seizures ($n = 79$).

For the purposes of this report, we excluded those with a single recorded seizure and those with acute symptomatic seizures (i.e., occurring within 90 days of a precipitating cerebral

injury). This resulted in 558 individuals with recurrent unprovoked epileptic seizures, i.e., epilepsy.¹⁹

The initial round of data collection carried out between 1984 and 1987 elicited data on basic demographics and clinical characteristics. Additional information was sought on all possible somatic and psychiatric comorbidities. This final set of queries used pointed (i.e., requiring an affirmative or negative response) and open-ended questions (i.e., requiring a free-text response), instructing GPs to record any additional conditions the individual may have. There were a total of 12 rounds of data collection on participant comorbidities, up until 2001. Following this, after the passage of the UK Data Protection Act of 1998²⁰ and the Health and Social Care Act of 2001,²¹ the collection of comorbidity data was expressly not allowed during the 2009 follow-up. A single study author (M.R.K.) reviewed the reported comorbidities and coded the associated ICD-10 chapter²² and the date when it was first reported. The 10th version of the ICD is a system developed and supported by the WHO that classifies human disease into 20 different categories. Comorbidities that were only listed on the death certificates were not included in this analysis as this would have created a bias differential to those who have died.

All individuals in the NGPSE have been flagged at the UK National Health Service (NHS) Information Centre and the investigators are sent a copy of the death certificate whenever a person dies. This ensures complete mortality ascertainment, assuming that the participant dies within the territorial boundaries of the United Kingdom or that the NHS was notified of the death if the participant died elsewhere. Each death certificate respects the WHO's recommended format and includes fields for recording up to 3 CODs as well as field II (i.e., "Other significant conditions contributing to the death").²³ We included all deaths occurring up until October 5, 2009, in this report.

Only selected data related to the distribution of CODs from the NGPSE have been reported.^{1, 24, 25} Previously we identified one primary COD based upon the clinical judgment of the investigators, frequently using the first condition described on the death certificate. Now we present complete COD data and strictly distinguish between underlying COD and immediate COD. The distinction between these 2 types of COD reflects which condition initiated a series of events leading to death (i.e., the underlying COD) vs the condition that occurred only just prior to death (i.e., immediate COD). The Sixth Decennial International Revision Conference of the WHO resolved that the underlying COD be reported as the main COD in all official reporting.^{23,}

²⁶ Care was taken to record the underlying COD according to the General Principle and selection rules as laid out in the ICD-10 manual.²³ As such, pneumonia and pulmonary embolism were considered immediate CODs unless there were no other CODs listed on the death certificate, in which case they were recorded as “pneumonia or pulmonary embolism not otherwise specified.” Cardiac or respiratory failure is a mode of death and not a COD²³; if no other condition was listed on the death certificate, the underlying and immediate CODs were coded as “Other.” Vascular dementia was coded as dementia rather than cerebrovascular disease. Each COD was described as a proportionate mortality rate (PMR), where the numerator was the number of deaths due to a particular COD and the denominator the total number of deaths within the NGPSE.²⁷

The underlying epilepsy etiology was characterized for all individuals. This was done using data provided by GPs up until the timing of the diagnostic panel. One study author (M.R.K.), unaware of any other characteristic of each person, including the timing of death, determined whether the underlying COD was directly related to the epilepsy etiology for that individual (e.g., due to a primary cerebral neoplasm or to cerebrovascular disease). Death from an external cause was generally not considered related to post-traumatic epilepsy unless these were the same event.

Statistical analyses

Differences in proportions were tested using 2-sided Fisher exact test. A Holms-Bonferroni correction was used to control for the effect of multiple comparisons.²⁸

Cox proportional hazards regression was used to model associations between each ICD comorbidity chapter and all-cause mortality. Each ICD chapter was first regressed using a simple model where age (categorized into approximate quartiles) at the time of the index seizure (the event that led to presenting to medical attention) and sex were included as covariates. ICD chapters found to have a $p < 0.10$ in the simple model were included in the fully adjusted model, along with age at the time of the index seizure, participant sex, and early epilepsy remission (defined as an absence of seizures more than 1 year after the index event). The period at risk for each participant began with the time of the index seizure and ended with the time of death or, if alive, October 5, 2009. With the exception of ICD chapters 16 and 17, which are by definition congenital, each ICD chapter was treated as a categorically time-varying covariate with the

exposure beginning when it was first reported to the NGPSE investigators. Schoenfeld residuals were used to confirm the proportionality assumption in the fully adjusted regression models.²⁹

We used additional regression models to investigate the individual comorbid conditions contained within those ICD chapters that were significant predictors of all-cause mortality (in the fully adjusted ICD chapter models) as well as those that were of particular clinical interest (e.g., all neurologic and psychiatric diseases). Simple and fully adjusted regression models were carried out in a similar manner to that for the ICD chapters.

STATA/SE, version 12.0 (StataCorp LP, College Station, TX) was used to conduct all statistical analyses.

Standard protocol approvals, registrations, and patient consents. The NGPSE was approved by the National Research Ethics Committee (reference 07/H0720/160) and the National Information Governance Board Ethics and Confidentiality Committee (PIAF 1–05[g]/2008 NGPSE). The requirement for individual participant consent was waived.

RESULTS

The clinical characteristics and demographics of the cohort are presented in table 1. There were 190 deaths during the follow-up period although the death certificate for one person was not available (who was therefore excluded from the COD-related analyses).

Table 1: Study participant characteristics (n = 558)

Characteristic	Result ^a
Male sex	291 (52)
Epilepsy etiology	
Remote symptomatic	132 (24)
Idiopathic/cryptogenic	426 (76)
Early epilepsy remission ^b	183 (33)
All-cause mortality	190 (34) ^c
Age at index seizure (years)	
Entire cohort	24.4 (13.8, 56.1) ^d
Alive	17.1 (9.6, 27.4)
Dead	64.2 (50.8, 75.1)
Age at last follow up (years)	
Entire cohort	47.4 (36.8, 70.9)
Alive	40.9 (33.3, 51.1)
Dead	74.8 (59.1, 83.1)
Duration of follow-up (years)	
Entire cohort	23.0 (14.9, 24.2)
Alive	23.9 (23.0, 24.7)
Dead	8.1 (2.3, 15.2)

^a Variables presented as n (%) or median (IQR).

^b Defined as no recurrent seizures more than one year after the index event.

^c One death certificate was missing and so this individual was excluded from the COD-related analyses.

^d Thirty-eight percent of individuals (212/558) were aged less than 18 years.

The distribution of underlying CODs is depicted in figure 1A. A majority of deaths were due to non- cerebral neoplasm, cardiovascular disease, or cerebrovascular disease (58.7% or 111/189), while external causes (4.2% or 8/189) and epilepsy-related causes (e.g., sudden unexplained death in epilepsy [SUDEP] or status epilepticus) (3.2% or 6/189) accounted for a minority. Twenty-nine percent (12/41) of the fatal noncerebral neoplasms were responsible for an individual's epilepsy as a result of metastatic disease. Underlying CODs within the "other"

category included chronic alcoholism, hepatic encephalopathy, diabetes mellitus, hypertension, systemic amyloidosis, endocarditis, nephropathy, peripheral vascular disease, and ischemic bowel disease.

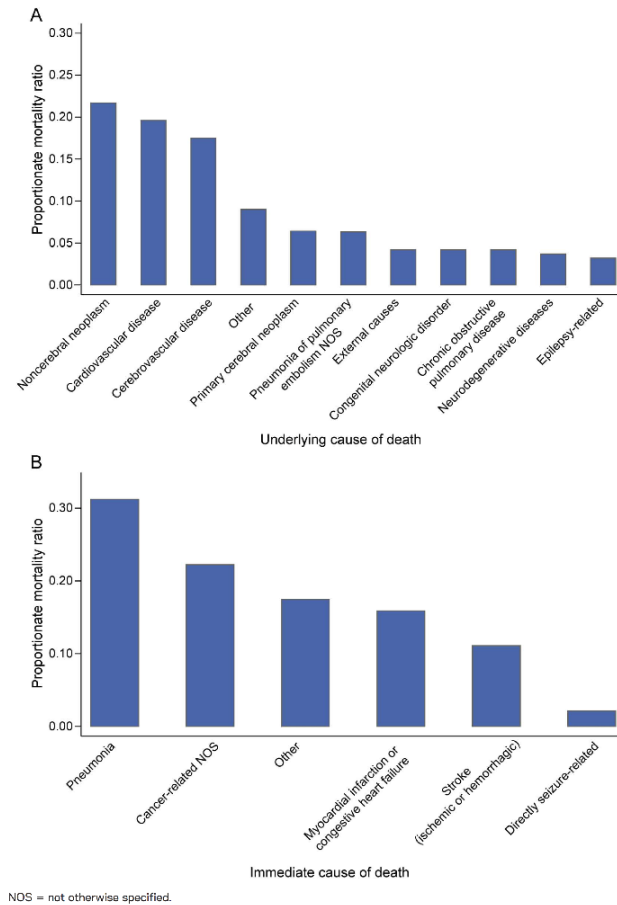


Figure 1: Proportionate mortality ratio for underlying (A) and immediate (B) cause of death

The distribution of immediate CODs is shown in figure 1B. Pneumonia was the most common immediate COD (31.2% or 59/189). Among individuals whose immediate COD was pneumonia, the underlying CODs were cerebrovascular disease (22.0% [13/59]), other (17%

[10/59]), noncerebral neoplasm (13.6% [8/59]), congenital neurologic disorder (11.9% [7/59]), cardiovascular disease (8.5% [5/59]), neurodegenerative disease (8.5% [5/59]), and epilepsy-related (3.4% [2/59]). Among 9 (4.8%) individuals who died of pneumonia, an underlying COD was not indicated on the death certificate.

There were no evident differences in the proportions of each underlying COD when stratified by timing of death (≤ 2 years vs > 2 years after the index seizure) (table e-1 on the *Neurology*® Web site at Neurology.org). People age 60 years or younger at the time of the index seizure as well as those age 60 years or younger at the time of death were more likely to die of primary cerebral neoplasm (15.1% vs 0.9%, $p < 0.011$, and 21.3% vs 1.4%, $p < 0.011$, respectively) but were less likely to die of cerebrovascular disease (2.7% vs 26.7%, $p < 0.011$, and 4.3% vs 21.8%, $p < 0.032$, respectively) (table e-1). People age 60 years or younger at the time of death were also more likely to die of external causes (12.8% vs 1.4%, $p = 0.03$) or a congenital neurologic disorder (12.8% vs 1.4%, $p = 0.03$).

We found that in 22.8% (43/189) of deaths, the underlying COD was directly related to the individual's epilepsy etiology. This proportion was as high as 57.5% during the first 2 years of follow-up, decreasing to 6.0% after > 15 years of follow-up (figure 2, with further details in table e-2). Overall, among people dying within 2 years of their index seizure, there was a more than fourfold greater chance that the cause of their epilepsy was directly related to their underlying COD (percent ratio 4.28, 95% confidence interval [CI] 2.63–6.97; $p < 0.0001$) as compared to people who died more than 2 years after their index seizure. The epilepsy etiologies of the 189 individuals who died are listed in table e-3.

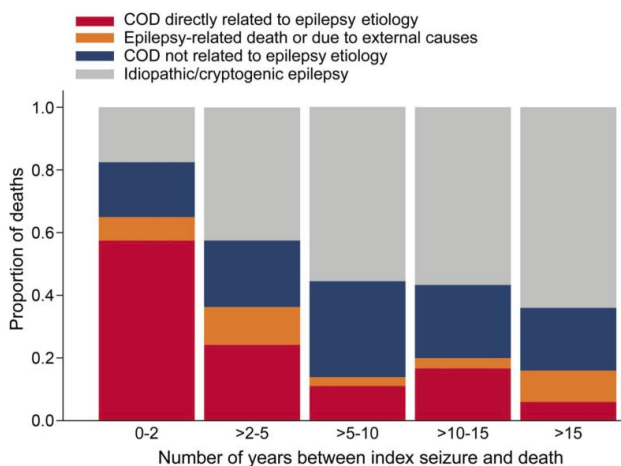


Figure 2. Relationship between epilepsy aetiology and underlying cause of death (COD)

The results of our survival analyses examining for predictors of mortality are presented in tables 2 and 3. Male sex was found to be protective, with a roughly 30% decrease in the risk of death (adjusted hazard ratios [HRs] 0.69 and 0.70). Early epilepsy remission was also protective (adjusted HRs 0.61 and 0.66).

Of the comorbidities of epilepsy, ICD chapters 2 (neoplasms), 4 (endocrine, nutritional, and metabolic diseases), 13 (diseases of the musculoskeletal system and connective tissue), 17 (congenital malformations, deformations, and chromosomal abnormalities), and 19/20 (injury, poisoning, and certain other consequences of external causes/external causes of morbidity and mortality) were significant predictors of mortality (table 2). ICD chapter 13 was the only chapter whose presence predicted a decreased risk of mortality (adjusted HR 0.42 [95% CI 0.19–0.91]).

Table 2: Predictors of mortality (n = 558)

Predictor	Simple models ^a		Fully adjusted model ^{a,b}	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at index seizure (years)				
<15 (n=161)	Reference	.	Reference	.
15 to <30 (n=152)	1.56 (0.67, 3.66)	0.302	1.74 (0.74, 4.10)	0.206
30 to <60 (n=123)	9.55 (4.70, 19.39)	<0.001	10.48 (5.09, 21.56)	<0.001
≥60 (n=122)	52.69 (26.46, 104.92)	<0.001	67.98 (33.09, 139.64)	<0.001
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	0.69 (0.51, 0.92)	0.013
Early epilepsy remission ^c (n=183)	0.73 (0.53, 1.00)	0.047	0.61 (0.44, 0.83)	0.002
ICD-10 chapters^d				
1 – Certain infectious and parasitic diseases (n=11)	1.62 (0.22, 11.88)	0.633		
2 – Neoplasms (n=55)	3.05 (1.67, 5.57)	<0.001	2.72 (1.47, 5.04)	0.001
3 – Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (n=15)	1.36 (0.60, 3.11)	0.461		
4 – Endocrine, nutritional and metabolic diseases (n=41)	3.10 (1.54, 6.21)	0.001	3.36 (1.65, 6.82)	0.001
5 – Mental and behavioral disorders (n=135)	1.19 (0.77, 1.83)	0.429		
6 – Diseases of the nervous system (n=83)	1.29 (0.68, 2.46)	0.437		
7 – Diseases of the eye and adnexa (n=12)	0.47 (0.11, 1.90)	0.286		
8 – Diseases of the ear and mastoid process (n=9)	n/a ^e	.		
9 – Diseases of the circulatory system (n=119)	1.09 (0.68, 1.75)	0.710		
10 – Diseases of the respiratory system (n=54)	1.27 (0.59, 2.73)	0.539		
11 – Diseases of the digestive system (n=37)	1.49 (0.82, 2.71)	0.188		
12 – Diseases of the skin and subcutaneous tissue (n=26)	1.10 (0.27, 4.48)	0.893		
13 – Diseases of the musculoskeletal system and connective tissue (n=32)	0.46 (0.21, 0.99)	0.048	0.41 (0.19, 0.88)	0.022
14 – Diseases of the genitourinary system (n=18)	1.09 (0.40, 2.95)	0.872		

15 – Pregnancy, childbirth and the puerperium (n=7)	n/a ^c	.		
16 – Certain conditions originating in the perinatal period (n=10)	3.35 (0.78, 14.4)	0.105		
17 – Congenital malformations, deformations and chromosomal abnormalities (n=13)	4.84 (1.92, 12.18)	0.001	5.20 (2.06, 13.16)	<0.001
18 – Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (n=13)	1.84 (0.68, 4.97)	0.229		
19/20 – Injury, poisoning and certain other consequences of external causes/ External causes of morbidity and mortality (n=45)	2.62 (1.21, 5.69)	0.015	2.67 (1.21, 5.92)	0.015

^a All models included age at index seizure and sex as covariates.

^b This model also included early epilepsy remission as well as any ICD-10 chapter that was found to have a $p < 0.10$ in the simple models.

^c Defined as no recurrent seizures more than one year after the index event.

^d International Classification of Diseases, version 10, classifying human disease into 20 broad categories.

^e Not available; could not be calculated due to collinearity.

Examining the constituents of selected ICD chapters, primary cerebral and noncerebral neoplasms, dementia, Parkinson disease, cerebrovascular disease, traumatic brain injury, and substance abuse were significant and independent predictors of mortality (table 3).

Table 3: Expanded ICD-10 chapters as predictors of mortality (n = 558)

Predictor	Simple models ^a		Fully adjusted model ^{a,b}	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at index seizure (years)				
<15 (n=161)	Reference	.	Reference	.
15 to <30 (n=152)	1.56 (0.67, 3.66)	0.302	1.95 (0.81, 4.65)	0.134

30 to <60 (n=123)	9.55 (4.70, 19.39)	0.001	11.16 (5.31, 23.45)	<0.001
≥60 (n=122)	52.69 (26.46, 104.92)	<0.001	59.23 (27.89, 125.78)	<0.001
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	0.70 (0.52, 0.95)	0.021
Early epilepsy remission (n=183)	0.73 (0.53, 1.00)	0.047	0.66 (0.48, 0.93)	0.016
ICD chapter 2 ^c				
Primary cerebral neoplasm (n=22)	4.36 (2.65, 7.17)	<0.001	5.02 (2.99, 8.43)	<0.001
Non-cerebral neoplasm (n=34)	3.08 (1.68, 5.65)	<0.001	4.22 (2.25, 7.89)	<0.001
ICD chapter 4				
Diabetes mellitus, obesity or hypercholesterolemia (n=30)	2.77 (1.21, 6.39)	0.016	1.17 (0.41, 3.33)	0.762
Other (n=14)	2.77 (1.11, 6.95)	0.029	2.12 (0.68, 6.58)	0.194
ICD chapter 5				
Depression (n=42)	0.55 (0.26, 1.19)	0.131		
Anxiety (n=11)	1.09 (0.26, 4.46)	0.909		
Substance abuse (n=27)	3.63 (1.33, 9.88)	0.012	5.42 (1.92, 15.26)	0.001
Dementia (n=41)	2.30 (1.32, 4.00)	0.003	2.75 (1.51, 5.01)	0.001
Learning disability (n=22)	2.58 (1.11, 6.03)	0.028	2.10 (0.86, 5.12)	0.104
Other (n=20)	1.65 (0.21, 12.88)	0.630		
ICD chapter 6				
Migraine (n=30)	1.77 (0.76, 4.10)	0.186		
Parkinson's disease (n=8)	3.53 (1.40, 8.88)	0.007	5.09 (1.99, 13.02)	0.001
Focal neurological deficit (n=11)	1.05 (0.14, 7.57)	0.964		
Other (n=34)	0.95 (0.35, 2.61)	0.926		
ICD chapter 9				
Cerebrovascular disease (n=53)	2.93 (1.47, 5.83)	0.002	3.96 (1.96, 8.04)	<0.001
Cardiac disease (n=45)	1.13 (0.65, 1.96)	0.674		
Hypertension (n=37)	1.10 (0.44, 2.74)	0.843		
Other (n=20)	1.46 (0.68, 3.14)	0.9184		
ICD chapter 13				

Inflammatory musculoskeletal disease (n=14)	0.23 (0.03, 1.62)	0.139		
Degenerative musculoskeletal disease (n=13)	0.55 (0.22, 1.35)	0.190		
Other (n=5)	0.94 (0.13, 6.80)	0.951		
ICD chapter 17				
Congenital malformations, deformations and chromosomal abnormalities (n=13)	4.84 (1.92, 12.18)	0.001	4.89 (1.85, 12.87)	0.001
ICD chapter 19/20				
Traumatic brain injury (n=32)	5.67 (1.34, 23.98)	0.018	9.80 (2.30, 41.68)	0.002
Any fracture without brain injury (n=9)	2.52 (0.92, 6.90)	0.073	2.06 (0.71, 5.95)	0.182
Other (n=4)	1.27 (0.17, 9.22)	0.816		

^a All models included age at index seizures and sex as covariates.

^b This model also included early epilepsy remission as well as any comorbidity that was found to have a $p < 0.10$ in the simple models.

^c The number with each comorbidity will not necessarily equate with those numbers presented in Table 2, given that a single individual may have more than one comorbidity within each chapter.

DISCUSSION

The NGPSE is one of the largest prospective community-based cohorts with almost 25 years follow-up examining the risk and determinants of mortality among people with epilepsy.^{2, 4, 30} Prior analyses of the NGPSE have reported the overall standardized mortality ratio (SMR) for all-cause mortality, stratified by age, timing after the index seizure, and epilepsy etiology, as well as SMRs for selected CODs.^{1, 24, 25} In this article, we report 3 novel main findings. First, we describe the complete distribution of CODs, distinguish between underlying and immediate CODs, and demonstrate that the majority of deaths (59%) were due to noncerebral neoplasms (only 29% of which were related to the epilepsy etiology), cardiovascular disease, and cerebrovascular disease, while epilepsy-related causes accounted for only 3% of deaths. Pneumonia was the most important immediate COD, representing what is likely a common

terminus in a fatal sequence of events. Second, we demonstrate that overall 23% of underlying CODs were directly related to an individual's epilepsy etiology and that this was fourfold as likely to be the case if death occurred within 2 years of the index seizure. Third, we demonstrate that several somatic and psychiatric comorbidities are predictive of mortality. When examining specific conditions, neoplasms (primary cerebral and noncerebral neoplasm), several neurologic diseases (dementia, Parkinson disease, cerebrovascular disease, and traumatic brain injury), and substance abuse were independently associated with increased mortality risk.

The majority of deaths in our cohort were due to noncerebral neoplasms, cardiovascular disease, and cerebrovascular disease, while relatively few were epilepsy-related. It is difficult to compare PMRs between populations but our findings are generally comparable to others in high-income countries. A previous meta-analysis reported that 4% of deaths in low-risk groups of people with epilepsy are due to SUDEP³¹ (generally considered to be the most common cause of epilepsy-related death).³² Our findings emphasize that comorbidities similar to those responsible for mortality in the general population³³ are also the most important mediators of premature death in people with epilepsy. The increased risk of mortality from these diseases may be related to the postulated pro-neoplastic effect of certain antiepileptic drugs¹ or the increased risk of metabolic syndrome with others.³⁴ It may also be that epilepsy is a surrogate in some instances for severe neoplastic or atherosclerotic disease, where individuals with more severe forms of these comorbidities are more likely to develop epilepsy as well as die prematurely. In either case, at the level of the general population, physician counseling of people with epilepsy with regards to neoplastic and atherosclerotic risk factors appears to be as important as counseling individuals on the risk of SUDEP or status epilepticus, if not more so.

Only one other study has investigated the relationship between epilepsy etiology and COD, showing that in the first year of follow-up, 72.2% (39/54) of CODs among those with remote symptomatic epilepsy were related to the underlying epilepsy etiology.¹⁴ We now confirm these findings, doing so with a much larger cohort than the previous investigators. We additionally demonstrate that this relationship between underlying COD and epilepsy etiology weakens over time, which may explain why mortality rates similarly decrease over time.¹

We report a number of comorbid conditions that significantly and independently predict mortality in the NGPSE. One recent study reported that a life-time history of certain psychiatric disorders (including substance abuse) predicted increased risk of death from external causes

(largely suicide and accidental death).¹¹ We now demonstrate that a lifetime history of substance abuse is a significant predictor of not only death due to external causes but all-cause mortality.

Our findings show that male sex was associated with a 30% decrease in mortality risk, after controlling for age, early epilepsy remission, and comorbidities. This is somewhat surprising as male sex is typically associated with a shorter life expectancy.³⁵ This merits further study.

Our study has a number of strengths. The NGPSE is a prospective community-based cohort of people with both adult and childhood-onset epilepsy, allowing for a complete spectrum of people, and has an exceptionally long period of follow-up. Our method of assessing whether an individual has died or not probably captured all deaths. Finally, we carefully defined underlying and immediate COD for each participant (using the official death certificate but generally without the benefit of an autopsy), while following rules as described by the WHO, which is an important distinction if one's ultimate goal is to interrupt the fatal sequence of events leading to death.²³

Our study has limitations. The NGPSE relied upon GP reporting of psychiatric and somatic comorbidities, via a combination of pointed and open-ended questions. These data were sampled on 12 occasions, up to 2001, after which no further comorbidity information could be collected. We expect that misclassification of each participant's comorbidity status (including failure to report an existing comorbidity) was probably independent of their eventual survival outcome. As a result, any bias would have led to an underestimation rather than an overestimation of the associated risk, and therefore any significant findings are likely to be true. The NGPSE also relied upon the history and records provided by GPs in the 1980s to establish the etiology of each person's epilepsy without the benefit of modern imaging techniques. This inevitably means that some individuals labeled as having cryptogenic epilepsy would have a declared etiology if the study were repeated today. Practically speaking, however, the repetition of such a study seems remote given the current research environment and requirements for individual consent, at least in the United Kingdom.

This study presents a number of important findings related to improving our understanding of the determinants of premature mortality in epilepsy. These findings represent important opportunities for future research and potential avenues for preventative strategies and initiatives.

AUTHOR CONTRIBUTIONS

M.R.K., G.S.B., and J.W.S. designed the study. M.R.K., A.N., G.S.B., and J.N. collected the data. M.R.K. carried out the statistical analyses and drafted the manuscript. M.R.K., G.S.B., A.N., J.N., and J.W.S. critically revised the manuscript. All approved the final version. J.W.S. is the guarantor.

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SUPPORTING INFORMATION

Table e-1: Underlying cause of death, stratified by timing and age

Underlying cause of death	Proportionate mortality ratio	Percent difference	p-value ^a
Non-cerebral neoplasm			
Overall (n=189) ^b	21.7		
Death ≤2 years after index seizure (n=40)	32.5	13.7	0.829
Death >2 years after index seizure (n=149)	18.8		
Aged ≤60 years at time of index seizure (n=73)	26.0	7	>0.999
Aged >60 years at time of index seizure (n=116)	19.0		
Aged ≤60 years at time of death (n=47)	17.0	-6.2	>0.999
Aged >60 years at time of death (n=142)	23.2		
Cardiovascular disease			
Overall (n=189)	19.6		
Death ≤2 years after index seizure (n=40)	10.0	-12.2	>0.999
Death >2 years after index seizure (n=149)	22.2		
Aged ≤60 years at time of index seizure (n=73)	13.7	-9.6	0.931
Aged >60 years at time of index seizure (n=116)	23.3		
Aged ≤60 years at time of death (n=47)	10.6	-11.9	0.636
Aged >60 years at time of death (n=142)	22.5		
Cerebrovascular disease			
Overall (n=189)	17.5		
Death ≤2 years after index seizure (n=40)	20.0	3.2	>0.999
Death >2 years after index seizure (n=149)	16.8		
Aged ≤60 years at time of index seizure (n=73)	2.7	-24	<0.011
Aged >60 years at time of index seizure (n=116)	26.7		
Aged ≤60 years at time of death (n=47)	4.3	-17.5	0.032
Aged >60 years at time of death (n=142)	21.8		
Other			
Overall (n=189)	9.0		
Death ≤2 years after index seizure (n=40)	5.0	-5.1	>0.999
Death >2 years after index seizure (n=149)	10.1		
Aged ≤60 years at time of index seizure (n=73)	9.6	1	>0.999
Aged >60 years at time of index seizure (n=116)	8.6		

Aged ≤60 years at time of death (n=47)	8.5	-0.7	>0.999
Aged >60 years at time of death (n=142)	9.2		
Primary cerebral neoplasm			
Overall (n=189)	6.4		
Death ≤2 years after index seizure (n=40)	12.5	7.8	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	15.1	14.2	<0.011
Aged >60 years at time of index seizure (n=116)	0.9		
Aged ≤60 years at time of death (n=47)	21.3	19.9	<0.011
Aged >60 years at time of death (n=142)	1.4		
Pneumonia or pulmonary embolism NOS			
Overall (n=189)	6.4		
Death ≤2 years after index seizure (n=40)	0.0	-8.1	0.814
Death >2 years after index seizure (n=149)	8.1		
Aged ≤60 years at time of index seizure (n=73)	5.5	-1.4	>0.999
Aged >60 years at time of index seizure (n=116)	6.9		
Aged ≤60 years at time of death (n=47)	4.3	-2.7	>0.999
Aged >60 years at time of death (n=142)	7.0		
External causes			
Overall (n=189)	4.2		
Death ≤2 years after index seizure (n=40)	5.0	1	>0.999
Death >2 years after index seizure (n=149)	4.0		
Aged ≤60 years at time of index seizure (n=73)	8.2	6.5	0.456
Aged >60 years at time of index seizure (n=116)	1.7		
Aged ≤60 years at time of death (n=47)	12.8	11.4	0.03
Aged >60 years at time of death (n=142)	1.4		
Congenital neurological disorder			
Overall (n=189)	4.2		
Death ≤2 years after index seizure (n=40)	2.5	-2.2	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	9.6	8.7	0.054
Aged >60 years at time of index seizure (n=116)	0.9		
Aged ≤60 years at time of death (n=47)	12.8	11.4	0.03
Aged >60 years at time of death (n=142)	1.4		
Chronic obstructive pulmonary disease			
Overall (n=189)	4.2		

Death ≤2 years after index seizure (n=40)	2.5	-2.2	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	4.1	-0.2	>0.999
Aged >60 years at time of index seizure (n=116)	4.3		
Aged ≤60 years at time of death (n=47)	2.1	-2.8	>0.999
Aged >60 years at time of death (n=142)	4.9		
Neurodegenerative diseases			
Overall (n=189)	3.7		
Death ≤2 years after index seizure (n=40)	7.5	4.8	>0.999
Death >2 years after index seizure (n=149)	2.7		
Aged ≤60 years at time of index seizure (n=73)	1.4	-3.8	>0.999
Aged >60 years at time of index seizure (n=116)	5.2		
Aged ≤60 years at time of death (n=47)	0	-4.9	0.984
Aged >60 years at time of death (n=142)	4.9		
Epilepsy-related			
Overall (n=189)	3.2		
Death ≤2 years after index seizure (n=40)	2.5	-0.9	>0.999
Death >2 years after index seizure (n=149)	3.4		
Aged ≤60 years at time of index seizure (n=73)	4.1	1.5	>0.999
Aged >60 years at time of index seizure (n=116)	2.6		
Aged ≤60 years at time of death (n=47)	6.4	4.3	0.984
Aged >60 years at time of death (n=142)	2.1		

^a Holms-Bonferroni corrected p-values.

^b Of 190 deaths, one death certificate was missing and so the cause of death could not be determined.

Table e-2: Relationship between underlying cause of death and epilepsy etiology, stratified by timing of death

Number of years between index seizure and death (n)	Number of deaths directly related to epilepsy etiology (%)	Number of epilepsy-related deaths or due to external causes (%)	Number of deaths not related to epilepsy etiology (%)	Number of people with idiopathic / cryptogenic epilepsy (%) ^a
0-2 (40)	23 (57.5)	3 (7.5)	7 (17.5)	7 (17.5)

>2-5 (33)	8 (24.2)	4 (12.1)	7 (21.2)	14 (42.4)
>5-10 (36)	4 (11.1)	1 (2.8)	11 (30.6)	20 (55.6)
>10-15 (30)	5 (16.7)	1 (3.3)	7 (23.3)	17 (56.7)
>15 (50)	3 (6.0)	5 (10.0)	10 (20.0)	32 (64.0)

^a The relationship between the underlying cause of death and epilepsy etiology could not be determined given that the epilepsy etiology was unknown.

Table e-3: Epilepsy etiology among participants who have died (n = 189)^a

Etiology	n (%)
Cerebrovascular	61 (32.3)
Primary cerebral or non-cerebral neoplasm	21 (11.1)
Alcohol or drug abuse	4 (2.1)
Post traumatic	3 (1.6)
Congenital or genetic	6 (3.2)
Post encephalitis	1 (0.5)
Perinatal injury	1 (0.5)
Other	1 (0.5)
Unknown/idiopathic	91 (48.1)

^a The epilepsy etiology of the one individual with a missing death certificate was alcohol-related.

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