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Running title: Mortality in people with epilepsy

ABSTRACT

The risk of premature mortality is increased in people with epilepsy. The reasons for this and how it may relate to epilepsy aetiology remain unclear. The National General Practice Study of Epilepsy is a prospective, community-based cohort that includes 558 people with recurrent unprovoked seizures and almost 25 years of follow-up. In this study the underlying and immediate causes of death are described as well as their relationship to epilepsy aetiology and epilepsy-related causes of death. Predictors of mortality were examined using adjusted Cox proportional hazards models, with a particular emphasis on the psychiatric and somatic comorbidities of epilepsy. We found that the three most common underlying causes of death were neoplasm, cardiovascular and cerebrovascular disease, accounting for the majority of deaths (58.8% or 111/189) while epilepsy-related causes accounted for 3.2% (6/189) of deaths. Pneumonia was the most common immediate causes of death and accounted for 31.2% (59/189) of deaths. Overall, in 22.8% of individuals, the underlying causes of death was directly related to the epilepsy aetiology, although this differed significantly depending on whether the death occurred within two years of the index seizure or later [percent ratio=4.28 (95% confidence interval: 2.63, 6.97)]. The adjusted models demonstrated that International Classification of Diseases-10 chapters 2, 4, 13, 17 and 19 / 20 were significant predictors of mortality. Specific comorbidities associated with increased mortality were: primary cerebral neoplasm, non-cerebral neoplasm, substance abuse, dementia, Parkinson's disease and traumatic brain injury. Our findings suggest particular lines of investigation and intervention for the future which may serve to stem the tide of premature mortality in epilepsy.

KEYWORDS: Epilepsy, mortality, cause of death, comorbidity

ABBREVIATIONS:

Cause of death (COD)

Confidence interval (CI)

General practitioners (GP)

Hazard ratio (HR)

International Classification of Diseases (ICD)

Interquartile range (IQR)

National General Practice Study of Epilepsy (NGPSE)

People with epilepsy (PWE)

Proportionate mortality ratio (PMR)

Sudden unexplained death in epilepsy (SUDEP)

United Kingdom (UK)

INTRODUCTION

Recent work has highlighted that PWE suffer from premature mortality relative to the general population. This has been shown in high-income countries such as the UK[1], USA[2], Sweden[3] and Iceland[4] as well as low- to middle-countries such as Bolivia[5], India[6] and China.[7] The reasons for this are not readily apparent. Prior studies have described the distribution of the CODs in PWE but few distinguished between underlying and immediate causes.[7-13] There is a paucity of data examining the relationship between epilepsy aetiology and COD.[14, 15] There also have been attempts to describe predictors of premature mortality in people, including non-adherence 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 of epilepsy in predicting mortality in a cohort of PWE.

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

MATERIAL AND METHODS

The NGPSE is a longitudinal cohort study of incident epileptic seizures with almost 25 years of follow-up, the methods of which have been previously described.[1, 18] Briefly, the subjects of the NGPSE were initially identified between June 1984 and October 1987 by 275 participating GPs from across the UK who had been asked to report any person of any age with newly suspected epileptic seizures. A diagnostic panel subsequently reviewed all potential participants and

identified those with definite or probable/possible epileptic seizures. Of the initial 1195 people registered by their GP, the diagnostic panel concluded that 792 (66.3%) had had epileptic seizures. The remaining individuals were diagnosed with either febrile seizures (n=220), pre-existing epilepsy or neonatal seizures (n=104), or no clear history of epileptic seizures (n=79) and have been excluded from the present report.

For the purposes of this report we further excluded those with a single recorded epileptic seizure (and at least 12 months of follow-up) as well as those with acute symptomatic seizures (occurring within 90 days of a precipitating cerebral injury, as per the consensus during the NGPSE's initial design). This resulted in a cohort of 558 individuals with recurrent unprovoked epileptic seizures.

Following the initial assessment between 1984 and 1987, there were approximately annual follow-ups by NGPSE investigators with each individual's GP up to 1997 after which there were two more follow-ups, in 2001 and 2009. In general, no direct contact was made by NGPSE investigators with individual study participants. With the initial assessment and each subsequent follow-up, data were collected on basic demographics and features of each person's seizures. In addition to these epilepsy-related queries, additional information was sought on all possible somatic and psychiatric comorbidities. This final set of queries used pointed questions about the presence of a number of conditions which were considered especially relevant at the time of the NGPSE's initial design (meningitis/encephalitis, stroke, intra-cranial surgery, head injury with loss of consciousness, alcohol or drug abuse) but also instructed GPs to record any additional condition(s) the individual may have. This information was elicited from the GPs on 12 occasions, up until 2001. Following this, after the passing of the UK Data Protection Act of 1998 and the Health and Social Care Act of 2001, new individual consent requirements were

applied to the NGPSE, requirements that created insurmountable barriers to the continued collection of comorbidity data. A single study author (MRK) reviewed the reported comorbidities and coded the associated ICD-10 chapter [19] as well as the date when it was first reported.

All individuals in the NGPSE have been flagged at the UK National Health Service (NHS) Information Centre. The study investigators are therefore notified whenever any person dies and are sent a copy of the death certificate. This ensures complete mortality ascertainment, assuming that the subject dies within the territorial boundaries of the UK, or that the NHS was notified of their death if they died elsewhere. Each death certificate respects the World Health Organisation's recommended format and includes fields for recording up to three CODs[20] Each death certificate also includes field II (i.e. "Other significant conditions contributing to the death…"). All deaths occurring up until the 5th October 2009 are included in this report.

Only selected data related to the distribution of CODs from this cohort have been previously reported.[1, 21, 22] Previously, our research group also did not explicitly distinguish between underlying and immediate COD but instead identified one COD based upon the clinical judgement of the investigators while reviewing the contents of the death certificate. In the present study, we present complete COD data and strictly distinguish between underlying COD and immediate COD. The distinction between these two types of COD reflects our understanding of which condition initiated a series of events leading to death (i.e. the underlying COD) versus the condition which occurred only just prior to death (i.e. immediate COD). The Sixth Decennial International Revision Conference of the World Health Organisation resolved that the underlying COD be reported as the main COD in all official reporting.[20, 23] Care therefore was taken for the purposes of this study by one author (MRK) to record the underlying COD according the to the

"General Principle" and selection rules as laid out in the ICD-10 manual.[20] 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, as described in the ICD-10, and not a COD; if no other condition was listed on the death certificate, the underlying COD was coded as "Other". Vascular dementia was coded as dementia rather than cerebrovascular disease. Each COD was described as a PMR, where the numerator is the number of deaths due to a particular COD and the denominator is the total number of deaths in the same population and period.[24]

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

Statistical analyses

Any differences in proportions were tested using two-sided Fisher's exact test. A Holms-Bonferroni correction was used to control for the effect of multiple comparisons.[25] Continuous variables are presented as median (IQR) due to heavily skewed distributions rendering means difficult to interpret.

Cox proportional hazards regression were used to model associations between each ICD-10 comorbidity chapter and all-cause mortality. Additional comorbidities that were only listed on the death certificates were not included in this analysis since this would have created a systematic source of error (i.e. information bias) differential to those who have, versus have not, died. Each ICD-10 chapter was first regressed using a simple model where age at the time of the index seizure (the event that lead to their presenting to medical attention; categorized into approximate quartiles) and sex were included as covariates. ICD-10 chapters found to have a p-value <0.10 in the simple model were included in the fully adjusted model, along with age at the time of the index seizure, subject sex and early seizure remission (defined as an absence of seizures more than one year after the index event). The period at risk for each subject began with the time of the index seizure and ended with the time of death or, if alive, the 5th October 2009. With the exception of chapters 16 and 17 which are by definition congenital and therefore present at the beginning of the period at risk, each ICD-10 chapter was treated as a categorically time-varying covariate with the exposure to each chapter beginning when it was first reported to the NGPSE investigators. These analyses allowed us to account for differences in the duration of exposure to each comorbidity. Schoenfeld residuals were used to confirm that the proportionality assumption was met for each regression model.[26] The assumption was considered violated when the global test was associated with a p-value <0.05. The categorical covariate early epilepsy remission (defined as no recurrent seizures after one year of follow up) was transformed to vary linearly with time in order to correct for a violation of the proportionality assumption.

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

The NGPSE was approved by the National Research Ethics Committee (REC Reference: 07/H0720/160); individual informed consent was again not required by the ethics committee.

RESULTS

The clinical characteristics and demographics of the cohort are presented in Table 1. Median age at the time of the index seizure was 24.4 years (IQR: 13.8, 56.1) and 291 (52%) were men. There were 190 deaths during the follow-up period (i.e. up to 5th October 2009) although the death certificate was not available for one person. Median age at last follow-up was 40.9 years (IQR: 33.3, 51.1) for those still alive at last follow-up and 74.8 years (59.1, 83.1) for those who died (i.e. their age at the time of death). One hundred eighty-three (32%) individuals did not have any recurrent seizures after 1 year since the index seizure (i.e. early epilepsy remission). Median duration of follow-up was 23.9 years (IQR: 23.0, 24.7) for those still alive at last follow-up.

The distribution of the underlying CODs is depicted in Fig. 1A. A majority of deaths were due to non-cerebral neoplasm, cardiovascular or cerebrovascular disease (58.8% or 111 of 189) while external causes and epilepsy-related (e.g. SUDEP or status epilepticus) accounted for only 4.2% (8 of 189) and 3.2% (6 of 189), respectively. Fifty-two percent of the non-cerebral neoplasms were responsible for an individual's epilepsy as a result of metastatic disease.

The distribution of the immediate CODs is depicted in Fig. 1B. Pneumonia was the most common immediate COD and accounted for 31.2% (59 of 189) of all deaths. Among individuals whose immediate COD was pneumonia, the underlying CODs were: 13 (22.0%) with cerebrovascular disease, 10 (17.0%) with other, eight (13.6%) with non-cerebral neoplasm, seven (11.9%) with congenital neurological disorder, five (8.5%) with cardiovascular disease, five

(8.5%) with neurodegenerative disease and two (3.4%) were epilepsy-related. For nine (4.8%) individuals who died of pneumonia, an underlying COD was not indicated on the death certificate.

In Fig. 2, the underlying CODs are stratified by timing of death (Fig. 2A) as well as age at the time of the index seizure (Fig. 2B) and time of death (Fig. 2C). After correcting for the effect of multiple comparisons, there were no evident differences in the proportions of each underlying COD when stratified by timing of death (≤2 years versus >2 years after the index seizure) with non-significant p-values throughout (Supplementary Table 1). People aged less than 60 years at the time of the index seizure as well as those aged less than 60 years at the time of death were more likely to die of primary cerebral neoplasm [15.1% versus 0.9% (p-value <0.010), and 21.3% versus 1.4% (p-value <0.010), respectively] or a congenital neurological disorder [9.6% versus 0.9% (p-value=0.048), and 12.8% versus 1.4% (p-value=0.003), respectively] but were less likely to die of cerebrovascular disease [2.7% versus 26.7% (p-value <0.010) and 4.3% versus 21.8% (p-value <0.028), respectively] with a similar but non-significant trend in cardiovascular disease (Fig. 2B-2C and Supplementary Table 1). People aged less than or equal to 60 years at the time of death were also more likely to die of external causes (12.8% versus 1.4%, p-value=0.027).

We found that in 22.8% (43 of 189) of deaths, the underlying COD was directly related to the individual's epilepsy aetiology (43.4% if the 90 individuals with idiopathic/cryptogenic epilepsy are excluded). This proportion was as high as 57.5% during the first 2 years of follow-up (69.7% if the seven individuals with idiopathic/cryptogenic epilepsy are excluded), decreasing over time to as low as 6.0% at >15 years of follow-up. (Fig. 3 with further details in Supplementary Table 2). Overall, among people dying within two years of their index seizure,

there was a more than four-fold greater chance that the cause of their epilepsy was directly related to their underlying COD [percent ratio (95% CI) =4.28 (2.63, 6.97); p-value<0.0001] as compared to people who died more than two years after their index seizure. The epilepsy aetiologies of the 190 individuals who died are listed in Supplementary Table 3.

The results of our survival analyses examining for predictors of mortality are presented in Tables 2 and 3. Age was the strongest predictor of death, where people aged 60 years or more at the time of the index seizure were on average 67 times more likely to die than people aged less than 15 years [adjusted HR: 66.92 (95% CI: 32.55, 137.59)]. Surprisingly, male sex was found to be protective, with a 30% decrease in the risk of death (adjusted HR: 0.69 (95% CI: 0.51, 0.93). There was no evidence that early epilepsy remission was predictive of mortality.

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)].

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

DISCUSSION

The NGPSE is one of the few and largest prospective community-based cohorts of PWE with almost 25 years follow-up examining the risk and determinants of mortality among PWE.[2, 4, 27] Prior analyses of the NGPSE have reported the overall SMR for all-cause mortality, stratified by age group, timing after index seizure and epilepsy aetiology, as well as SMRs for selected CODs.[1, 21, 22] We report three new main findings. First, we describe the complete distribution of CODs, distinguishing between underlying and immediate CODs, and demonstrate that the majority of deaths (59%) are due to non-cerebral neoplasms (48% of which were not the cause of the person's epilepsy), cardiovascular and cerebrovascular disease while epilepsy-related causes account for only 3% of deaths. We demonstrate that pneumonia is the most important immediate COD, representing what is likely a common terminus in a morbid sequence of events. Second, we demonstrate that overall 23% of underlying CODs are directly related to an individual's epilepsy aetiology and that this is four-fold more likely to be the case if death occurs within two years of the index seizure. Third, we demonstrate that certain somatic and psychiatric comorbidities are predictive of mortality among PWE. When categorized by ICD-10 chapter: neoplasms, endocrine, nutritional and metabolic diseases, congenital malformations, deformations and chromosomal abnormalities as well as injury, poisoning and external causes are associated with an increased risk of death while diseases of the musculoskeletal system and connective tissue are associated with decreased risk. When examining specific conditions, primary cerebral and non-cerebral neoplasms, substance abuse, dementia, Parkinson's disease, cerebrovascular disease and traumatic brain injury were independently associated with increased mortality risk.

A number of studies have described an overall increased risk of premature mortality among PWE relative to people without epilepsy.[2-7] Previous analyses of the NGPSE have

reported elevated SMRs, most recently reporting an overall standardized mortality ratio (SMR) of 2.2 (95% CI: 2.0, 2.5), an increase in premature mortality that was evident even 25 years after the index seizure.[1] That said, the reasons for this increase in mortality remain unclear and warrant urgent investigation.

The majority of deaths in our cohort were due to non-cerebral neoplasms, cardiovascular and cerebrovascular disease while relatively few were epilepsy-related. It is difficult to compare PMRs between populations given that it is not possible to control for differences in age, sex and calendar time. That said, our findings are generally similar to others in high-income countries, where a previous meta-analysis reported that 4% of deaths in low-risk groups of PWE are due to SUDEP,[28] but are remarkably different from studies limited to low or middle-income countries where approximately 20 to 75% of deaths are due to status epilepticus or SUDEP.[9, 29] This likely reflects the high proportion of idiopathic/cryptogenic epilepsy, ready access to necessary AEDs as well as the high proportion of seizure remission [30] seen in high-income relative to low or middle-income countries, the absence of all of which have both been associated with an increased risk of SUDEP.[27, 28]

Only one other study has investigated the relationship between epilepsy aetiology and COD, showing that after one year of follow-up, 72.2% (39 of 54) of CODs among those with remote symptomatic epilepsy were related to the underlying epilepsy aetiology.[14] Thanks to our much longer period of follow-up, we have additionally shown that this likelihood is significantly greater in the case of early deaths (i.e. within two years of the index seizure) versus those that occur later.

We report a number of comorbid conditions that significantly and independently predicted mortality in the NGPSE, including: both primary cerebral and non-cerebral neoplasms,

a history of substance abuse, dementia, Parkinson's disease, cerebrovascular disease and traumatic brain injury. One recent study reported that a lifetime history of any psychiatric disorders (including substance abuse) predicted increased risk of death from external causes (largely suicide and other accidents).[11] We did not examine for predictors of external causes of death but demonstrate that a lifetime history of substance abuse was a significant predictor of not only external causes of death but all-cause mortality.

Our study has a number of strengths. The NGPSE is a community-based cohort where participants were recruited from GP practices across the UK, allowing for a complete spectrum of PWE, and has an exceptionally long, almost 25-year period of follow-up. Our method of assessing whether an individual has died or not likely captured all deaths. Finally, we carefully defined underlying and immediate COD for each participant, using rules as described by the World Health Organisation, which is an important distinction if one's ultimate goal is to interrupt the sequence of morbid events leading to death.[20]

Our study has limitations. The NGPSE relied upon GP reporting of psychiatric and somatic comorbidities during the course of 12 different sampling periods between participant recruitment and 2001. It is possible that GP reporting was not complete. Since all of our comorbidity data were reported prior to anyone's death, misclassification of each subject's comorbidity status was likely independent (i.e. non-differential) to their eventual survival outcome. As a result, any bias would have led to an under-estimation of the associated risk and not over-estimation. The NGPSE also relied upon the history and records provided by GPs in the 1980s to establish the aetiology of each person's epilepsy without the benefit of modern imaging techniques. This likely means that some individuals labelled as having cryptogenic epilepsy would have a declared aetiology if the study were repeated today. Practically speaking, however,

this eventuality seems unlikely given the current research environment and requirements for individual consent, at least in the UK.

This study presents a number of important findings related to improving our understanding of the determinants of premature mortality among PWE. These findings represent important opportunities for future research and potential avenues to intervene in the morbid sequence of events that may lead to death.

TABLES

Table 1: Study subject characteristics (n=558)

Characteristic		Result[a]
Male sex		291 (52)
Early epilepsy remission[b]		183 (32)
All-cause mortality		190 (34)
Age at index seizure (years)		
	Entire cohort	24.4 (13.8, 56.1)
	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] Categorical variables are presented as n (%) while continuous variables are presented as median (IQR)

[b] Defined as no recurrent seizures more than 1 year after the index event

Table 2: Predictors of mortality (n=558)

Predictor	**Simple model[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	1.75 (0.74, 4.14)	0.199
30 to <60 (n=123)	**9.55 (4.70, 19.39)**	**<0.001**	**10.68 (5.18, 22.01)**	**<0.001**
≥60 (n=122)	**52.69 (26.46, 104.92)**	**<0.001**	**66.92 (32.55, 137.59)**	**<0.001**
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	**0.69 (0.51, 0.93)**	**0.013**
Early seizure remission[c] (n=183)	0.95 (0.73, 1.22)	0.677	0.84 (0.65, 1.09)	0.198
ICD chapters				
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**	**2.62 (1.42, 4.82)**	**0.002**
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**	**3.34 (1.64, 6.78)**	**0.001**
5 – Mental and behavioural 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[d]	.		
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**	**0.42 (0.19, 0.91)**	**0.028**
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[d]	.		
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**	**5.43 (2.15, 13.75)**	**<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**	**2.72 (1.23, 6.00)**	**0.013**

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

[b] This model also included early seizure remission as well as any ICD-10 chapter that was found to have a p-value <0.10 in the simple models

[c] Defined as no recurrent seizures more than 1 year after the index event

[d] Not available; could not be calculated due to collinearity

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

Predictor	**Simple model[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	1.99 (0.83, 4.77)	0.122
30 to <60 (n=123)	**9.55 (4.70, 19.39)**	**0.001**	**11.34 (5.38, 23.90)**	**<0.001**
≥60 (n=122)	**52.69 (26.46, 104.92)**	**<0.001**	**59.16 (27.79, 125.97)**	**<0.001**
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	**0.70 (0.52, 0.95)**	**0.023**
Early seizure remission[c] (n=183)	0.95 (0.73, 1.22)	0.677	0.89 (0.68, 1.16)	0.393
ICD chapter 2				
Primary cerebral neoplasm (n=22)	**4.36 (2.65, 7.17)**	**<0.001**	**5.42 (3.24, 9.06)**	**<0.001**
Non-cerebral neoplasm (n=34)	**3.08 (1.68, 5.65)**	**<0.001**	**4.04 (2.17, 7.55)**	**<0.001**
ICD chapter 4				
Diabetes mellitus, obesity or hypercholesterolemia (n=30)	**2.77 (1.21, 6.39)**	**0.016**	1.22 (0.43, 3.42)	0.708
Other (n=14)	**2.77 (1.11, 6.95)**	**0.029**	2.03 (0.66, 6.22)	0.213
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**	**4.86 (1.74, 13.56)**	**0.003**
Dementia (n=41)	**2.30 (1.32, 4.00)**	**0.003**	**2.84 (1.56, 5.17)**	**0.001**
Learning disability (n=22)	**2.58 (1.11, 6.03)**	**0.028**	2.21 (0.90, 5.43)	0.083
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**	**4.59 (1.81, 11.68)**	**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**	**4.30 (2.13, 8.71)**	**<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	**4.84 (1.92, 12.18)**	**0.001**	**5.00 (1.89, 13.22)**	**0.001**
ICD chapter 19/20				
Traumatic brain injury (n=32)	**5.67 (1.34, 23.98)**	**0.018**	**9.09 (2.13, 38.72)**	**0.003**
Any fracture without brain injury (n=9)	2.52 (0.92, 6.90)	0.073	2.34 (0.82, 6.70)	0.112
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 seizure remission as well as any ICD-10 chapter that was found to have a p-value <0.10 in the simple models

FIGURE LEGENDS

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

Figure 2: Proportionate mortality ratio, stratified by timing of death (A) as well as age at time of index seizure (B) and death (C)

Legend: * Statistically significant difference with Holms-Bonferroni-corrected p-value <0.05

Figure 3: Relationship between epilepsy aetiology and underling cause of death

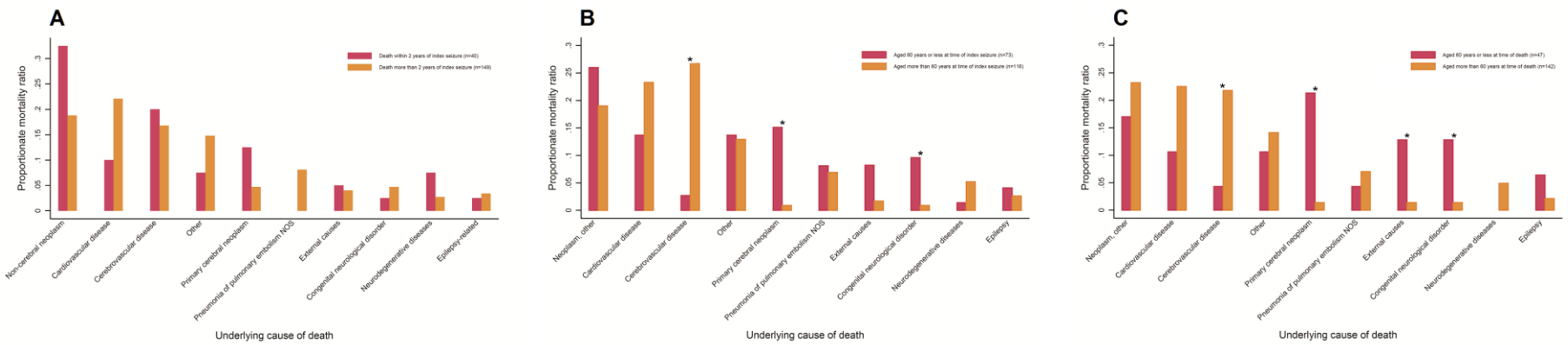
A
Proportionate mortality ratio
Death within 2 years of index seizure (n=40)
Death more than 2 years of index seizure (n=149)
Non-cerebral neoplasm
Cardiovascular disease
Cerebrovascular disease
Other
Primary cerebral neoplasm
Pneumonia of pulmonary embolism NOS
External causes
Congenital neurological disorder
Neurodegenerative diseases
Epilepsy-related
Underlying cause of death
B
Proportionate mortality ratio
Aged 60 years or less at time of index seizure (n=73)
Aged more than 60 years at time of index seizure (n=116)
Neoplasm, other
Cardiovascular disease
Cerebrovascular disease
Other
Primary cerebral neoplasm
Pneumonia of pulmonary embolism NOS
External causes
Congenital neurological disorder
Neurodegenerative diseases
Epilepsy
Underlying cause of death
C
Proportionate mortality ratio
Aged 60 years or less at time of death (n=47)
Aged more than 60 years at time of death (n=142)
Neoplasm, other
Cardiovascular disease
Cerebrovascular disease
Other
Primary cerebral neoplasm
Pneumonia of pulmonary embolism NOS
External causes
Congenital neurological disorder
Neurodegenerative diseases
Epilepsy
Underlying cause of death

Figure 1

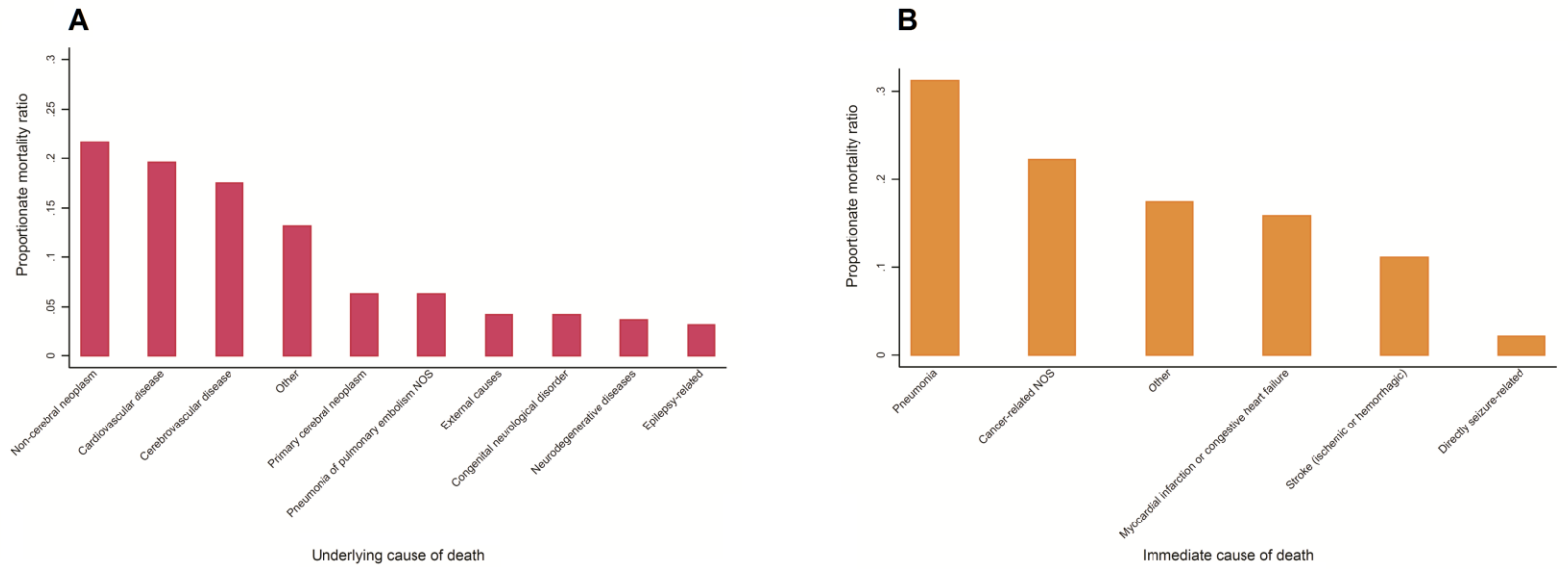
A
Proportionate mortality ratio
0
.05
.1
.15
.2
.25
.3
Non-cerebral neoplasm
Cardiovascular disease
Cerebrovascular disease
Other
Primary cerebral neoplasm
Pneumonia of pulmonary embolism NOS
External causes
Congenital neurological disorder
Neurodegenerative diseases
Epilepsy-related
Underlying cause of death
B
Proportionate mortality ratio
0
.1
.2
.3
Pneumonia
Cancer-related NOS
Other
Myocardial infarction or congestive heart failure
Stroke (ischemic or hemorrhagic)
Directly seizure-related
Immediate cause of death

Figure 2

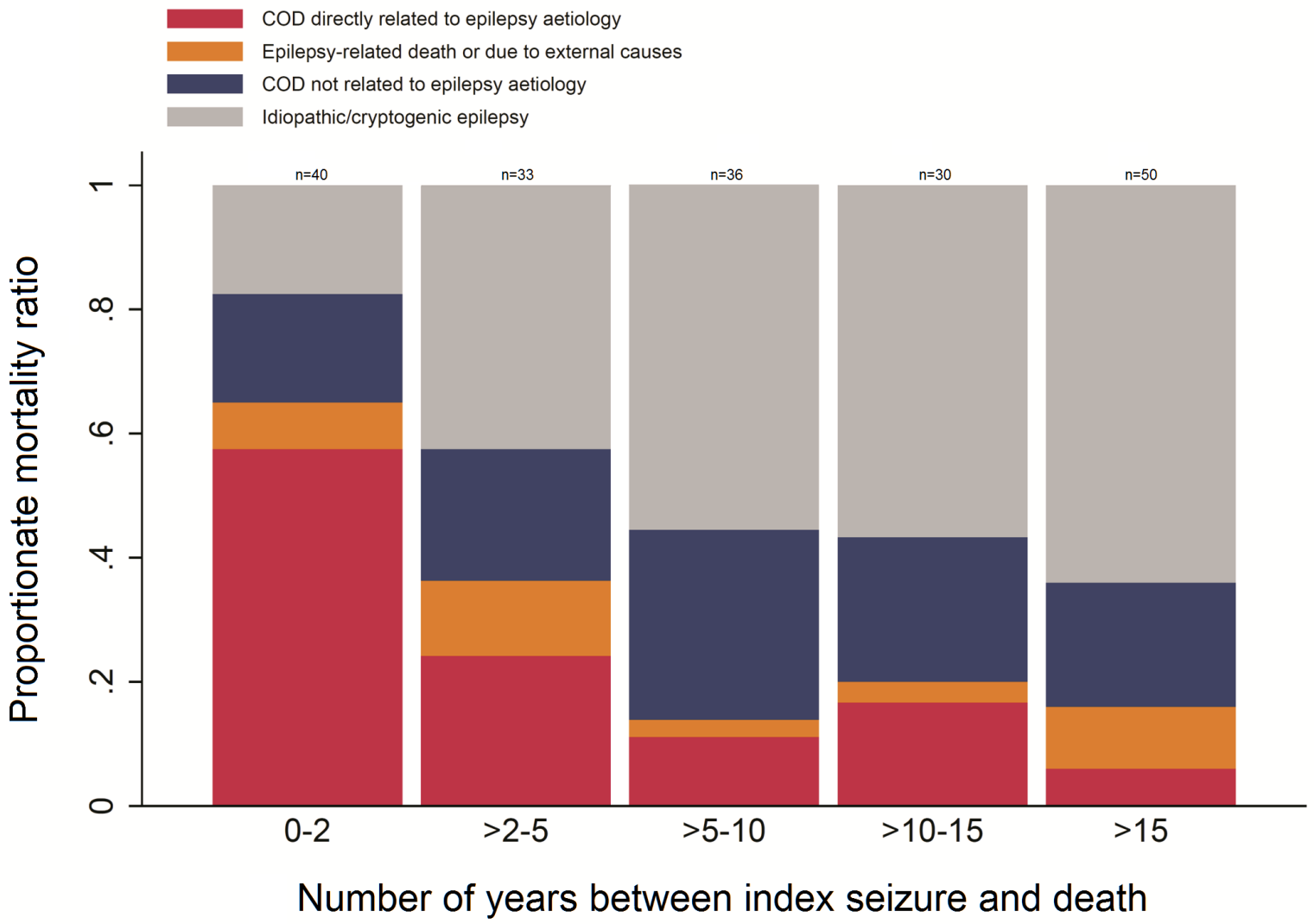
COD directly related to epilepsy aetiology
Epilepsy-related death or due to external causes
COD not related to epilepsy aetiology
Idiopathic/cryptogenic epilepsy
n=40
n=33
n=36
n=30
n=50
Proportionate mortality ratio
0
.2
.4
.6
.8
1
0-2
>2-5
>5-10
>10-15
>15
Number of years between index seizure and death

Figure 3

FUNDING

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Underlying cause of death, stratified by timing and age (n=189)[a]

Underlying cause of death	Proportionate mortality (%)	Percent difference	p-value[b]
Non-cerebral neoplasm			
Overall (n=189)	21.7		
Death ≤2 years after index seizure (n=40)	32.5	13.7	0.747
Death >2 years after index seizure (n=149)	18.8		
Aged ≤60 years at time of index seizure (n=73)	26.0	7.0	1.000
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	1.000
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	-12.1	0.920
Death >2 years after index seizure (n=149)	22.1		
Aged ≤60 years at time of index seizure (n=73)	13.7	-9.6	0.798
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	0.546
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	1.000
Death >2 years after index seizure (n=149)	16.8		
Aged ≤60 years at time of index seizure (n=73)	2.7	-24.0	**<0.010**
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	**0.028**
Aged >60 years at time of death (n=142)	21.8		
Other			
Overall (n=189)	13.2		
Death ≤2 years after index seizure (n=40)	7.5	-7.3	1.000
Death >2 years after index seizure (n=149)	14.8		
Aged ≤60 years at time of index seizure (n=73)	13.7	0.8	1.000
Aged >60 years at time of index seizure (n=116)	12.9		
Aged ≤60 years at time of death (n=47)	10.6	-3.5	1.000
Aged >60 years at time of death (n=142)	14.1		
Primary cerebral neoplasm			
Overall (n=189)	6.3		
Death ≤2 years after index seizure (n=40)	12.5	7.8	0.938
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	15.1	14.2	**<0.010**
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	**<0.010**
Aged >60 years at time of death (n=142)	1.4		
Pneumonia or pulmonary embolism NOS			
Overall (n=189)	6.3		
Death ≤2 years after index seizure (n=40)	0.0	-8.1	0.740
Death >2 years after index seizure (n=149)	8.1		
Aged ≤60 years at time of index seizure (n=73)	8.1	1.2	1.000
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	1.000
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	1.0	1.000
Death >2 years after index seizure (n=149)	4		
Aged ≤60 years at time of index seizure (n=73)	8.2	6.5	0.399
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	**0.027**
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	1.000
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	9.6	8.7	**0.048**
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	**0.027**
Aged >60 years at time of death (n=142)	1.4		
Neurodegenerative diseases			
Overall (n=189)	3.7		
Death ≤2 years after index seizure (n=40)	7.5	4.8	0.990
Death >2 years after index seizure (n=149)	2.7		
Aged ≤60 years at time of index seizure (n=73)	1.4	-3.8	1.000
Aged >60 years at time of index seizure (n=116)	5.2		
Aged ≤60 years at time of death (n=47)	0	-4.9	0.820
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	1.000
Death >2 years after index seizure (n=149)	3.4		
Aged ≤60 years at time of index seizure (n=73)	4.1	1.5	1.000
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	0.820
Aged >60 years at time of death (n=142)	2.1		

[a] Of 190 deaths, one death certificate was missing and so the cause of death could not be determined

[b] Holms-Bonferroni corrected *p*-values

Supplementary Table 2: Relationship between underlying cause of death and epilepsy, stratified by timing of death (n=189)[a]

Number of years between index seizure and death (n)	Number of deaths directly related to epilepsy aetiology (%)	Number of epilepsy-related or deaths or due to external causes (%)	Number of deaths not related to epilepsy aetiology (%)	Number of people with idiopathic/cryptogenic epilepsy (%)[b]
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] Of 190 deaths, one death certificate was missing and so cause of death could not be determined

[b] The relationship between the underlying cause of death and epilepsy aetiology could not be determined given that the epilepsy aetiology was unknown

Supplementary Table 3: Epilepsy aetiology among subjects who have died as of 5 October 2009 for whom data was available (n=189)[a]

Aetiology	**n (%)**
Cerebrovascular	61 (32.3)
Neoplasm	21 (11.1)
EtOH or drug abuse	4 (2.1)
Post traumatic	3 (1.6)
Congenital or genetic	6 (3.2)
Other	1 (0.5)
Post encephalitis	1 (0.5)
Perinatal injury	1 (0.5)
Unknown/idiopathic	91 (48.2)

[a] This is the number of deaths where the death certificate was available. The epilepsy aetiology of the one individual with a missing death certificate was alcohol-related

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