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Epilepsy and mortality: a retrospective cohort analysis with a nested case–control study identifying causes and risk factors from primary care and linkage-derived data

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ABSTRACT

Objectives People with epilepsy (PWE) have a higher mortality rate than the general population. Epilepsy-related deaths have increased despite all-cause mortality decreasing in the general population pre-COVID-19. We hypothesised that clinical and lifestyle factors may identify people more at risk.

Design We used a retrospective cohort study to explore cause of death and a nested case–control study to identify risk factors.

Setting We explored factors associated with mortality using primary care population data from 1 April 2004 to 31 March 2014. Data were obtained from the Clinical Practice Research Datalink which compiles anonymised patient data from primary care in the UK. Cause of death data was supplemented from the Office of National Statistics when available.

Participants The analysis included 70 431 PWE, with 11 241 registered deaths.

Results The number of deaths within the database increased by 69% between the first and last year of the study. Epilepsy was considered as a contributing cause in approximately 45% of deaths of PWE under 35. Factors associated with increased risk of death included attendance at emergency departments and/or emergency admissions (OR 3.48, 95% CI 3.19 to 3.80), antiepileptic drug (AED) polytherapy (2 AEDs: OR 1.60, 95% CI 1.51 to 1.71; 3 AEDs: OR 2.06, 95% CI 1.86 to 2.29; 4+AEDs: OR 2.62, 95% CI 2.23 to 3.08), status epilepticus (OR 2.78, 95% CI 1.64 to 4.71), depression (OR 1.67, 95% CI 1.57 to 1.76) and injuries (OR 1.54, 95% CI 1.43 to 1.67). No seizures in the prior year (OR 0.52, 95% CI 0.41 to 0.65).

Conclusion Our results add to existing evidence that deaths in epilepsy are increasing. Future studies could focus on identifying PWE at high risk and addressing them with clinical interventions or better self-management. Identifying specific risk factors for younger people should be a priority as epilepsy may be a factor in close to half of deaths of PWE under 35 years of age.

INTRODUCTION

Epilepsy is one of the most common neurological conditions with about 50 million

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study examines the higher mortality rate in epilepsy by exploring risk factors that could be mitigated by interventions in clinical practice.
⇒ The study included data collected in primary care which is large and representative compared with hospital data.
⇒ The large sample size collected from participating UK practices contributes to the generalisability of the results.
⇒ The dataset used was from 2004 to 2014, as this covered a period where epilepsy was part of a national programme for outcome reporting.

people affected worldwide.[1] With access to good treatment, it is estimated that 60%–70% of people with epilepsy (PWE) can become free of seizure.[2] However, epilepsy is also an important cause of premature death.[3] Mortality rates of PWE are higher than for the general population.[4–9] A longitudinal cohort study from Sweden found that an epilepsy diagnosis was associated with a 14-fold increased risk of all-cause death.[5] Some studies suggest that this has not changed over time.[4 10] Other data suggest the number of deaths in PWE is increasing despite a decrease in all-cause mortality in the general population.[8 11 12] Public Health England reported that deaths with epilepsy as a contributing factor increased by 70% between 2001 and 2014, while all-cause deaths in the population decreased by 6%.[11]

Some causes of death in PWE are similar to the general population, such as circulatory and respiratory diseases, dementia, Alzheimer's and cancers.[11 13 14] Others are related to consequences of the condition itself such as injuries, burns and drowning during seizures.[5 9 15] Lifestyle and psychosocial factors

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contribute to increased risk of mortality and include alcohol or substance misuse,[13 16] low adherence to medication,[10] depression[5 16] and socioeconomic status.[11 16] Sudden unexpected death in epilepsy (SUDEP) is sometimes posited as a common cause of death for PWE. A recent review suggests SUDEP accounts for 12% of all-cause deaths in epilepsy.[10] However, factors that can be prevented or treated are under-researched and could lead to more impact on reducing mortality.

In 2011, our group published risk factors increasing mortality in PWE based on population data collected in primary care in the UK between 1993 and 2007.[16] Here, we follow up on the analysis using data collected during an incentivised programme which rewarded enhanced monitoring and care for PWE in primary care over 10 years. We hypothesised that the epilepsy data collected under this programme would be of high quality allowing for a comprehensive analysis of causes and risk factors associated with mortality. We report the number of deaths recorded during this time, the causes of death for younger and older PWE, and risk factors associated with mortality among PWE.

METHODS
Study design
A retrospective cohort design was used to analyse mortality and causes of death in PWE. Risk factors affecting mortality were analysed using a nested case–control study.

Setting
Data was obtained from the Clinical Practice Research Datalink (CPRD). This database contains anonymised patient data obtained from electronic records from primary care clinics in the UK. The data are sent from participating clinics to a central server where data is cleaned, checked for quality and curated. A study from 2015 counted 11 299 221 patients registered in the CPRD from 674 general practitioner (GP) practices.[17] Patients in the database were representative of the UK population when compared with the 2011 census.[17] For our study period, mid-year counts for 2004 show 4 584 065 patients were active in the database (alive and currently registered in a GP practice) with 50.1% being female. In 2013, 4 493 034 patients were active at mid-year and 50.4% were female.

Our study period was from 1 April 2004 to 31 March 2014 during which epilepsy management came under the Quality and Outcomes Framework (QOF), a programme implemented within the primary care setting. Revised QOF clinical indicators were implemented in April 2014 when most epilepsy indicators were discontinued. The aim of the programme was to incentivise improvement in the recording of clinical information on specific lifestyle items or long-term health conditions with the view that structured monitoring and reporting improved the quality of care.[18]

Types of data
The CPRD includes 'patient data' which include demographic information, 'clinical data' include information on clinical events such as diagnosis or symptoms, and 'additional clinical details' that include lifestyle factors. It also includes 'therapy data' which contain information on prescriptions, product codes, doses and treatment schedules. Clinical data are entered initially as alpha numeric Read codes by the GP into electronic medical records. These are converted into numeric Medcodes within the CPRD for easier analysis by researchers. Medication types are recorded in 'therapy data' as numeric Prodcodes.

Cause of death information was obtained when available through linked data for a subset of patients from England and Wales from the Office of National Statistics (ONS). The cause of death is presented using International Classification of Diseases (ICD)-10 diagnostic codes and offers the main cause and up to 15 contributing causes, if applicable. Date of death was available both from the CPRD and ONS data and the earliest date of the two was used if there were discrepancies. The Index of Multiple Deprivation (IMD) was also obtained for each patient's GP practice, which was used for control matching in the case-control study. Practice IMD data were 'most up to date' version when requested in 2018.

Cohort study participants
For the mortality and cause of death cohort study, adults with epilepsy were included who were least 18 years old at time of death. Epilepsy was defined as having a documented epilepsy diagnostic code or seizure code and at least two prescriptions of antiepileptic drugs (AEDs). Using a diagnostic or seizure code with prescription data has been validated to identify cases of epilepsy in routinely collected data.[19] Any patient with a diagnostic code of 'epilepsy resolved' was removed from the study (Medcodes 8385 and 12848, Read codes 2126000 and 212J.00). Codes used to identify epilepsy and seizures are presented in online supplemental table S1.

Case–control study participants
Since we were focusing on the specific 12-month period prior to date of death to establish preventable risk factors, we opted to use a nested case–control study design. Cases were defined as PWE within the cohort with a documented date of death between 1 April 2004 and 31 March 2014 with at least 12 months of data recorded in our study period (thus earliest data of death included was 1 April 2005). Controls were randomly matched at a ratio of 3:1 by sex, practice IMD, year of birth (±1 year). For cases aged 18, controls were matched for year of birth +1 year. Controls were alive for at least 12 months after the date of death of their matched case. The first analysis was conducted for the whole dataset and a second one used data from PWE under the age of 35.

Exposure variables

Potential variables were selected based on existing literature, items part of the QOF and others associated with lifestyle. Exposure data were refined based on the availability and reliability of data in the CPRD. Full description of variables and sources of data are included in online supplemental file 1. List of codes used for each variable can be found in online supplemental file 2. We assessed variables occurring in the 12 months prior to the case's date of death for emergency department visits or emergency admissions, number of AEDs, status epilepticus, depression, injury, smoking status and seizure freedom. History of comorbidity was taken from all available patient data for dementia and stroke. Missing data was considered as 'no' for binary outcomes except for smoking status where the last known status was used, as previously reported.[20] Variables that were considered but not included due to poor quality of data included alcohol and substance use.

Statistics

The number all-cause deaths recorded in the CPRD was calculated for complete calendar years (from 2005 to 2013) to allow for comparisons with previous publications. All other analyses used data from the full study period (1 April 2004 to 31 March 2014). The cause of death data was analysed two ways: (1) tabulating the main cause of death in PWE and (2) evaluating the proportion of deaths with epilepsy listed as a contributing cause. A contributing cause was defined as either the main cause or listed as a cause in any of the other 15 positions on the death certificate. The main causes of death are presented for younger and older PWE with 65 years as the cut-off. Deaths with epilepsy as a contributing cause were divided by age group. To track trends, an additional analysis of main cause of death by full calendar year is presented in supplemental material (online supplemental table S2).

Conditional logistic regression was used for the nested case–control study. Variables were included in the model following maximum likelihood and Akaike information criterion testing. Potential confounders such as age, sex and deprivation were addressed by control matching. Data are presented as ORs and 95% CIs. The analysis was conducted for the whole dataset and subsequently for the subset of PWE aged under 35.

The following interactions were tested: age and emergency visit/admission, age and injury, age and dementia, age and stroke, status epilepticus and emergency visit/admissions, number of AEDs and seizure freedom, prescription issue and number of AEDs, injury and emergency visit/admission.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
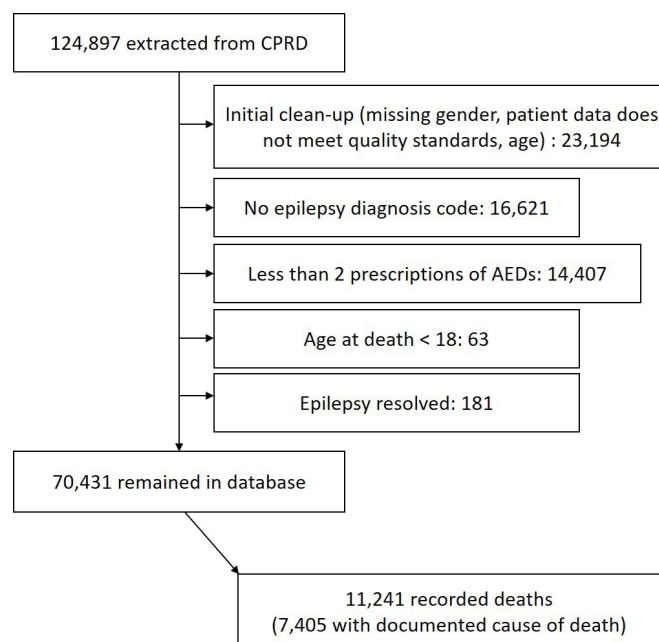

Figure 1 Flow chart of participant selection. AEDs, antiepileptic drugs; CPRD, Clinical Practice Research Datalink.

RESULTS

We obtained a sample size of 70 431 PWE with 11 241 who had a documented date of death within our time frame (figure 1). We obtained cause of death for 7405 people from ONS linked data. Age of patients ranged 18–105 with 50.8% male.

Number of deaths

The number of deaths recorded in the database increased between 2005 and 2013, from 821 to 1386 which represents a 68.8% increase (table 1). This increase was not attributed to more PWE being registered in the database as this decreased by 21.8% over the same period. The mean age of the participants within the database increased over time.

Cause of death

The main causes of death for PWE aged 18–64 years old were neoplasms (26.9%), diseases of the circulatory system (15.6%) and epilepsy (14.2%) (table 2A). For PWE 65 years and over, the main causes of death were diseases of the circulatory system (37.3%), neoplasms (17.2%) and diseases of the respiratory system (15.6%) (table 2B). Deaths due to epilepsy as a primary cause were documented in 2.7% of older PWE.

We tabulated the number of deaths with epilepsy listed as a cause of death, either the main or a contributing cause (table 3). In PWE under 35, almost 45% of deaths had epilepsy as a contributary cause (35.1%–53.3%, with a mean of 44.2%) (table 3). The trends are similar between sexes under 35 and over 65. However, they differ in the middle age. At the 40–44 age group, epilepsy-contributing deaths were twofold higher in male compared with female PWE.

Table 1 Number of recorded deaths of PWE in the CPRD per full year within the study period

	2005	2006	2007	2008	2009	2010	2011	2012	2013
Average age of adult PWE in the database, mean (SD)	48.7 (18.5)	49.0 (18.6)	49.3 (18.6)	49.6 (18.6)	49.9 (18.6)	50.2 (18.6)	50.5 (18.6)	50.8 (18.6)	51.2 (18.6)
No of PWE registered in the database	48447	48585	48031	46948	45941	44485	42521	40120	37865
No of recorded deaths	821	1075	1190	1241	1214	1307	1282	1386	1386
No of deaths per 1000 PWE in the CPRD	16.9	22.1	24.8	26.4	26.4	29.4	30.1	34.5	36.6

PWE defined as having an epilepsy diagnostic code and at least two prescriptions of AEDs, aged >17. Study period was from 1 April 2004 to 31 March 2014. Only data from full calendar years within this time frame were used for this table.
AED, antiepileptic drug; CPRD, Clinical Practice Research Datalink; PWE, people with epilepsy.

Table 2 Documented main cause of death of people with epilepsy (A) under 65 years (B) aged 65 and over

(A) ICD-10 category	Under 65, n (%)
Neoplasms (C00–D48)	571 (26.9)
Diseases of the circulatory system (I00–I99)	330 (15.6)
Epilepsy (G40–G41)	302 (14.2)
Diseases of the respiratory system (J00–J99)	176 (8.3)
Diseases of the nervous system (G00–G37, G43–G99), excluding epilepsy	164 (7.7)
Diseases of the digestive system (K00–KK93)	161 (7.6)
External causes of morbidity and mortality (V01–X59, X85–Y98)	129 (6.1)
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	70 (3.3)
Mental and behavioural disorders (F00–F99)	61 (2.9)
Endocrine, nutritional and metabolic diseases (E00–E90)	34 (1.6)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	29 (1.4)
External causes of morbidity and mortality (intentional) (X60–X84)	28 (1.3)
Diseases of the genitourinary system (N00–N99)	23 (1.1)
Certain infectious and parasitic diseases (A00–B99)	20 (0.9)
Diseases of the blood and blood-forming organs (D50–D89)	9 (0.4)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	9 (0.4)
Diseases of the skin and subcutaneous tissue (L00–L99)	4 (0.2)
Total	2120 (100.0)

(B) ICD-10 category	65 and over, n (%)
Diseases of the circulatory system (I00–I99)	1973 (37.3)
Neoplasms (C00–D48)	910 (17.2)
Diseases of the respiratory system (J00–J99)	827 (15.6)
Mental and behavioural disorders (F00–F99)	479 (9.1)
Diseases of the nervous system (G00–G37, G43–G99), excluding epilepsy	295 (5.6)
Diseases of the digestive system (K00–KK93)	173 (3.3)
Epilepsy (G40–G41)	142 (2.7)
Diseases of the genitourinary system (N00–N99)	130 (2.5)
External causes of morbidity and mortality (V01–X59, X85–Y98)	88 (1.7)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	86 (1.6)
Endocrine, nutritional and metabolic diseases (E00–E90)	67 (1.3)
Certain infectious and parasitic diseases (A00–B99)	46 (0.9)

Continued

Table 2 Continued

(B) ICD-10 category	65 and over, n (%)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	29 (0.5)
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	15 (0.3)
Diseases of the skin and subcutaneous tissue (L00–L99)	13 (0.2)
Diseases of the blood and blood-forming organs (D50–D89)	8 (0.2)
External causes of morbidity and mortality (intentional) (X60–X84)	4 (0.1)
Total	5285 (100.0)

ICD, International Classification of Diseases.

To explore whether there were changes in the causes of death over time, we tabulated the main cause of death by year (online supplemental table S2). Diseases of the circulatory system were consistently listed as the highest main cause of death for each year. The proportion of deaths due to mental and behavioural disorders doubled from 2011 onwards (mean percentage for 2005–2010: 5.05%, mean percentage for 2011–2013: 10.7%). The proportion of deaths attributed to epilepsy as the primary cause remained relatively stable throughout (6.3% for 2005 to 5.2% for 2013), although the number of deaths this represented increased (33 in 2005 to 51 to 2013).

Risk factors

Risk factors included in the model, frequencies and associated ORs are presented in table 4. Attendance at emergency departments in the previous 12 months was associated with the highest risk (OR 3.48, 95% CI 3.19 to 3.80). Compared with being prescribed one AED, prescription of two or more AEDs was associated with an elevated risk of death (2 AEDs: OR 1.60, 95% CI 1.51 to 1.71; 3 AEDs: OR 2.06, 95% CI 1.86 to 2.29; 4+AEDs: OR 2.62, 95% CI 2.23 to 3.08), while no AED prescription was associated with a lower risk (OR 0.77, 95% CI 0.68 to 0.87) (table 4). Other factors associated with an increased risk of mortality included experiencing status epilepticus within the past 12 months (OR 2.78, 95% CI 1.64 to 4.71), depression (OR 1.67, 95% CI 1.57 to 1.76), smoking (OR 1.45, 95% CI 1.35 to 1.56), injury (OR 1.54, 95% CI 1.43 to 1.67) and history of dementia (OR 1.39, 95% CI 1.26 to 1.53) and stroke (OR 1.07, 95% CI 1.01 to 1.14).

A lower risk of death was associated with seizure freedom in the previous 12 months (OR 0.52, 95% CI 0.41 to 0.65).

We found an interaction between having an emergency department visit or emergency admission and injury (OR 0.59, 95% CI 0.48 to 0.70).

As the cohort analysis of cause of death revealed epilepsy was a significant contributing factor of the cause of death in young PWE, we repeated the risk factor analysis for PWE aged under 35. Significant risk factors associated with risk of death included emergency department visit (OR 3.90, 95% CI 2.44 to 6.23), number of AEDs (no AEDs: 0.42, 95% CI 0.21 to 0.84, 2 AEDs: OR 1.72, 95% CI 1.23 to 2.40; 3 AEDs OR 2.37, 95% CI 1.52 to 3.67, 4+AEDs:

Table 3 Epilepsy documented as a contributing cause of death by age group

Age group	Male		Female	
	All cause deaths, n	Deaths with epilepsy as contributing cause, n (%) (95% CI)	All cause deaths, n	Deaths with epilepsy as contributing cause, n (%) (95% CI)
18–19	15	8 (53.3) (28.1 to 78.6)	8	3 (37.5) (4.0 to 71.0)
20–24	37	17 (45.9) (29.9 to 62.0)	29	13 (44.8) (26.7 to 62.9)
25–29	45	22 (48.9) (34.3 to 63.5)	37	17 (45.9) (29.9 to 62.0)
30–34	64	27 (42.2) (30.1 to 54.3)	37	13 (35.1) (19.8 to 50.5)
35–39	81	19 (23.5) (14.2 to 32.7)	62	17 (27.4) (16.3 to 38.5)
40–44	135	44 (32.6) (24.7 to 40.5)	75	12 (16.0) (7.7 to 24.3)
45–49	157	42 (26.8) (19.8 to 33.7)	104	18 (17.3) (10.0 to 24.6)
50–54	213	58 (27.2) (21.3 to 33.2]	114	19 (16.7) (9.8 to 23.5)
55–59	238	44 (18.5) (13.6 to 23.4)	165	23 (13.9) (8.7 to 19.2)
60–64	291	63 (21.6) (16.9 to 26.4)	213	36 (16.9) (11.9 to 21.9)
65–69	323	42 (13.0) (9.3 to 16.7)	266	38 (14.3) (10.1 to 18.5)
70–74	442	60 (13.6) (10.4 to 16.8)	295	34 (11.5) (7.9 to 15.2)
75–79	475	44 (9.3) (6.7 to 11.9)	444	57 (12.8) (9.7 to 15.9)
80–84	517	53 (10.3) (7.6 to 12.9)	578	68 (11.8) (9.1 to 14.4)
85–89	485	54 (11.1) (8.3 to 13.9)	623	62 (10.0) (7.6 to 12.3)
90–105	290	22 (7.6) (4.5 to 10.6)	547	65 (11.9) (9.2 to 14.6)

Table 4 Risk factors increasing mortality in PWE

Factor	Group	All				Age <35			
		Controls n (%)	Cases n (%)	OR	95% CI	Controls n (%)	Cases n (%)	OR	95% CI
Emergency department visit or emergency admission	No	25712 (94.2)	7469 (82.1)	Reference		875 (95.9)	252 (82.9)	Reference	
	Yes	1576 (5.8)	1627 (17.9)	3.48	3.19 to 3.80	37 (4.1)	52 (17.1)	3.90	2.44 to 6.23
No of AEDs prescribed	0	1667 (6.1)	353 (3.9)	0.77	0.68 to 0.87	107 (11.7)	10 (3.3)	0.42	0.21 to 0.84
	1	18768 (68.8)	5233 (57.5)	Reference		480 (52.6)	116 (38.2)	Reference	
	2	5196 (19.0)	2453 (27.0)	1.60	1.51 to 1.71	196 (21.5)	86 (28.3)	1.72	1.23 to 2.40
	3	1231 (4.5)	732 (8.0)	2.06	1.86 to 2.29	85 (9.3)	48 (15.8)	2.37	1.52 to 3.67
	4+	426 (1.6)	325 (3.6)	2.62	2.23 to 3.08	44 (4.8)	44 (14.5)	3.76	2.26 to 6.26
Status epilepticus	No	27261 (99.9)	9060 (99.6)	Reference					
	Yes	27 (0.1)	36 (0.4)	2.78	1.64 to 4.71				
Depression	No	21790 (79.9)	6158 (67.7)	Reference					
	Yes	5498 (20.1)	2938 (32.3)	1.67	1.57 to 1.76				
Smoking status	Non-smoker	23904 (87.6)	7579 (83.3)	Reference					
	Smoker	3384 (12.4)	1517 (16.7)	1.45	1.35 to 1.56				
Injury	No	24347 (89.2)	7579 (83.3)	Reference		864 (94.7)	270 (88.8)	Reference	
	Yes	2941 (10.8)	1517 (16.7)	1.54	1.43 to 1.67	48 (5.3)	34 (11.2)	1.99	1.19 to 3.31
Dementia	No	25698 (94.2)	8328 (91.6)	Reference					
	Yes	1590 (5.8)	768 (8.4)	1.39	1.26 to 1.53				
Stroke	No	21699 (79.5)	6960 (76.5)	Reference					
	Yes	5589 (20.5)	2136 (23.5)	1.07	1.01 to 1.14				
Age				1.15	1.11 to 1.19				
Seizure-free in previous 12 months	No	25180 (92.3)	8611 (94.7)	Reference		895 (98.1)	303 (99.7)	Reference	
	Yes	2108 (7.7)	485 (5.3)	0.52	0.41 to 0.65	17 (1.9)	1 (0.3)	0.17	0.02 to 1.44
Interaction: emergency department/admission × injury				0.59	0.48 to 0.70				

AED, antiepileptic drug; PWE, people with epilepsy.

OR 3.76, 95% CI 2.26 to 6.26), injury (OR 1.99, 95% CI 1.19 to 3.31) and seizure freedom (OR 0.17, 95% CI 0.02 to 1.44).

DISCUSSION
We examined the causes of death among PWE and risk factors associated with mortality in a group of PWE derived from primary care data. The number of PWE with recorded deaths increased throughout our 9-year study period while the deaths attributed to epilepsy remained stable. In our model, we found important factors associated with a higher risk of mortality, some of which could be identified and potentially ameliorated by step-up care.

There were differences in the proportion of deaths attributed to epilepsy between younger and older PWE. Studies have found deaths of younger PWE are more often attributed to epilepsy.[21][22] Indeed, epilepsy was the third highest main cause of death in younger PWE in our study, accounting for almost 15% of deaths. This increased to 35%–50% when evaluating all contributing causes in age groups under 35. As younger PWE tend to have less comorbidity than older adults, it may be simpler to attribute epilepsy as the main cause of death. New diagnoses of epilepsy in people over 65 are often secondary to cerebrovascular disease such as stroke or neoplasms in the brain.[23] In our study, dementia was found to increase the risk of death, which has been found to share biological links with epilepsy.[24] New-onset epilepsy in older people tends to be better controlled with AEDs.[25] Thus, other comorbidity may take precedence in older PWE when documenting the cause of death, as epilepsy contributed to only about 10% of deaths and was listed as a main cause in 3%.

Factors associated with increased risk of death
Our findings support evidence from previous studies. Factors associated with risk of mortality in epilepsy included: depression,[5][16][26] injuries,[3][5][9][16][27] dementia and stroke,[13][28] age[13] and seizure freedom.[3][13][15][16] Novel findings include increased risk associated with emergency department visits and/or emergency admissions, prescription of more than one AED, and status epilepticus. Status epilepticus is a known cause of death,[13][22][29] however, to our knowledge, it has not been included within a risk model before.

For the younger PWE group, emergency visit or emergency admissions, number of AEDs and injury were associated with higher risk of death. While, like the wider-sample, seizure freedom was associated with a lower risk of death.

Clinical implications
Epilepsy management
The need for better epilepsy management is at the core of our findings. Several risk factors are linked within this theme such as emergency department attendance, polypharmacy, injury and seizure freedom.

Visits to emergency departments or emergency admissions were associated with a threefold increased risk of death, the highest risk in our model. Visits to emergency services are associated with having injuries,[30] experiencing a seizure or a change in normal seizure presentation[31] and having less confidence in self-management.[32] Attendance at emergency departments for epilepsy could thus be considered a surrogate marker for poorer epilepsy control.[33] The National Audit of Seizure management in Hospitals, conducted during our study period in 2011 and 2013, found 63% of PWE presenting to emergency departments for seizures had not been seen by a specialist in the previous year.[34] Moreover only half of attendees were either seen by a neurologist on site or referred to one on discharge.[34] These are missed opportunities to follow up with patients who may be in need of clinical review and help with self-management, to mitigate their greater risk of death.

Areas for possible intervention
Regular medication review for people on multiple AEDs may be important as increased mortality risk was associated with two or more AEDs. Prescriptions of multiple AEDs may be an effect of having more refractory and harder to control epilepsy. However, polypharmacy may also result in more side effects and different treatment schedules which could lead to more problems with medication adherence.[35]

Depression has been reported in about 25% of PWE.[36][37] In our study, we found 30% of cases and 20% of controls had either a diagnosis of depression or a prescription of antidepressants. Depression and other psychiatric disorders have been found to be associated with worse quality of life[38] and affect self-management.[39] Many PWE have said they do not feel their mental health needs are being addressed and thus depression may be underassessed in this patient group.[40] As the proportion of deaths with psychiatric illness as a main cause increased twofold in our study period, psychiatric assessment and management should be provided for PWE.

Ultimately, the goal of better epilepsy management is seizure reduction or seizure freedom. Seizure freedom was associated with approximately a 50% reduced risk of mortality in our model. Previous findings showed seizure freedom conveyed similar mortality rates for PWE as those observed in the general population.[15]

Other factors
We explored lifestyle factors which may be associated with increased mortality and found smoking to be associated with a higher risk. Other findings may be less amenable to change, although some intervention may be helpful. For example, experiencing status epilepticus in the previous 12 months was associated with a higher risk of death. In epilepsy, it is most often associated with low blood levels of AEDs or alcohol misuse.[41] Injury to the brain (trauma, hypoxia, anoxia), tumours, infections and stroke can

also trigger status epilepticus and thus it may not be preventable.[41]

Strengths and limitations

The CPRD contains data collected from primary care which is vast and increased the generalisability of results as all participating UK practices were included. However, we relied on clinical data which has some limitations as compared with epidemiological studies. It is possible that a small number of cases might have been misclassified as having epilepsy but our case definitions of an epilepsy diagnostic code and AED prescription have been validated and used in previous studies.[16 19 42] Conversely, patients who presented to emergency departments or were managed only by hospital specialists might not have been included.

The quality of information in the CPRD is dependent on data entered by practice staff during consultations for clinical use, not for research purposes. Items not applicable for a patient may be left off, rather than recorded as such. In the case of diagnosis, there is no option for a GP to enter an absence of diagnosis. Missing data in routine primary care databases are not missing at random and thus statistical methods of dealing with missing data, such as multiple imputation, may not be appropriate.[43 44] For this reason, we interpreted missing data as 'no' or 'no complication', however, we recognise this may be a limitation for some factors. Other limitations include not knowing the cause of injuries or hospital attendance and thus they may be unrelated to epilepsy.

We defined the exposure variables based on previous studies, if available.[16 20 45] The CPRD information has been validated for long-term conditions, such as dementia and Alzheimer's disease, and for diagnoses made by hospital consultants.[46] As GPs issue prescriptions via electronic systems, the CPRD 'therapy data' has been found to be highly accurate for medication variables.[47] However, we included variables which may not have been previously validated such as injury and emergency department visit or emergency admission which is a limitation of this study. We explored other factors such as severe mental illness, self-injury, patient-level IMD, alcohol use, substance use, pregnancy and learning disability. These were found statistically not significant and not included in the final overall model or the under-35 model. We also investigated interactions between variables. While we found a significant interaction between emergency admissions and injuries, we did not find one with status epilepticus. This suggests that status epilepticus might have been under recorded as a reason for emergency department visits, and perhaps entered under a more general 'epilepsy' code within GP patient notes. However, these missing episodes of status would be captured by the emergency department admission variable, which was associated with the highest risk of death in our study. We hypothesise that accurate recording of status epilepticus would have further increased its associated risk with mortality.

The time frame of our analysis corresponded to the period where epilepsy was part of the QOF, a programme whereby GPs were contracted to record specific characteristics of their patients with epilepsy.[48] In particular, data on drug treatment, seizure frequency and seizure freedom were part of this programme.[48] We hypothesised that this would lead to better quality data for epilepsy and strengthen the study. While the data collected may be more complete than years prior, GP practices were less successful in achieving targets for epilepsy compared with other conditions, some of which are more highly rewarded.[48 49] Older data may contain outdated diagnoses of epilepsy which may not have been reconfirmed by today's standards, and if in remission, might not have been designated with an epilepsy resolved code. This could lead to missing epilepsy data. However, the strength of the CRPD is the vast data collected from the community setting compared with hospital databases or disease-specific registers.[19 42]

A limitation of our cohort study is the use of linked ONS data, which is only available for consenting individuals from England and Wales. Thus, data were not available for our whole cohort, and findings are not generalisable to Scotland and Northern Ireland. Death certificate data for epilepsy has often been found to be problematic. A 2002 audit of UK data found up to 40% of deaths were attributed to the wrong cause for PWE.[50] Epilepsy tends to be underestimated as a cause of death[8 26] and dismissed for other cardiovascular or respiratory explanations.[21 26 51] Indeed, we found other diseases were listed as primary cause of death which may in fact have been epilepsy. The percentage of deaths with epilepsy as a main cause remained stable throughout our study, suggesting that practice may not have changed during this time.

Research implications

Our initial risk factor model took into account PWE of all ages. However, as the main causes of death differ between younger and older PWE, risk factors may also be different. Thus, we repeated the analysis including PWE under the age of 35. Fewer of the variables were included in this model with the main differences being in lower ORs for having no AED prescription and being seizure free. The highest excess mortality due to epilepsy has been observed in younger people.[15] This would benefit from more research aiming to identify specific risks in younger PWE, particularly as we found epilepsy contributed to close to 50% of deaths in some younger age groups. We also did not evaluate potential causes of epilepsy, such as whether stroke or tumours preceded an epilepsy diagnosis, and whether this would impact mortality. In addition, the analysis may benefit from being repeated with more recent data from the CPRD and ONS.

CONCLUSION

Several reports, including ours, have shown deaths in epilepsy continue to rise. Epilepsy is deemed a contributing cause of death particularly in young PWE, but less so in

those over 65. While epilepsy in older people may be better controlled with AEDs, comorbidity may mask the impact of epilepsy. We found certain factors are associated with risk of death such as emergency department attendance and admission, AED polytherapy, depression and injuries. These could be addressed with clinical intervention and more information for self-management.

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SUPPLEMENTAL FILE 1

Codes used to identify epilepsy in the CPRD

Table S1. Codes used to identify epilepsy in the CPRD

medcode	readcode	readterm
573	F25..00	Epilepsy
85113	F250 A	
11186	F250.00	Generalised nonconvulsive epilepsy
2907	F250000	Petit mal (minor) epilepsy
1715	F250011	Epileptic absences
24309	F250200	Epileptic seizures - atonic
31830	F250300	Epileptic seizures - akinetic
34792	F250500	Lennox-Gastaut syndrome
59185	F250y00	Other specified generalised nonconvulsive epilepsy
44252	F250z00	Generalised nonconvulsive epilepsy NOS
26144	F251.00	Generalised convulsive epilepsy
95216	F2510	
988	F251000	Grand mal (major) epilepsy
22804	F251011	Tonic-clonic epilepsy
49340	F251111	Otohara syndrome
18471	F251200	Epileptic seizures - clonic
4801	F251300	Epileptic seizures - myoclonic
5152	F251400	Epileptic seizures - tonic
8187	F251500	Tonic-clonic epilepsy
45927	F251y00	Other specified generalised convulsive epilepsy
40806	F251z00	Generalised convulsive epilepsy NOS
9886	F252.00	Petit mal status
5117	F253.00	Grand mal status
4093	F253.11	Status epilepticus
32288	F254.00	Partial epilepsy with impairment of consciousness
3175	F254000	Temporal lobe epilepsy
23634	F254100	Psychomotor epilepsy
36203	F254200	Psychosensory epilepsy
55665	F254300	Limbic system epilepsy
34079	F254400	Epileptic automatism
11394	F254500	Complex partial epileptic seizure
31920	F254z00	Partial epilepsy with impairment of consciousness NOS
26015	F255.00	Partial epilepsy without impairment of consciousness
9569	F255000	Jacksonian, focal or motor epilepsy
5525	F255011	Focal epilepsy
65699	F255012	Motor epilepsy

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48134	F255100	Sensory induced epilepsy
73542	F255300	Visceral reflex epilepsy
98870	F255311	Partial epilepsy with autonomic symptoms
55739	F255400	Visual reflex epilepsy
68946	F255500	Unilateral epilepsy
40105	F255600	Simple partial epileptic seizure
26733	F255y00	Partial epilepsy without impairment of consciousness OS
27526	F255z00	Partial epilepsy without impairment of consciousness NOS
71719	F257.00	Kojevnikov's epilepsy
30604	F25B.00	Alcohol-induced epilepsy
30816	F25C.00	Drug-induced epilepsy
56359	F25D.00	Menstrual epilepsy
65673	F25E.00	Stress-induced epilepsy
30635	F25F.00	Photosensitive epilepsy
106571	F25H.00	Generalised seizure
6271	F25X.00	Status epilepticus, unspecified
38307	F25y.00	Other forms of epilepsy
55260	F25y000	Cursive (running) epilepsy
53483	F25y100	Gelastic epilepsy
9887	F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
25330	F25y300	Complex partial status epilepticus
96641	F25y500	Panayiotopoulos syndrome
9979	F25yz00	Other forms of epilepsy NOS
9747	F25z.00	Epilepsy NOS
3607	F25z.11	Fit (in known epileptic) NOS
99731	Fyu5000	[X]Other generalized epilepsy and epileptic syndromes
69831	Fyu5100	[X]Other epilepsy
59120	Fyu5200	[X]Other status epilepticus
71801	Fyu5900	[X]Status epilepticus, unspecified
4109	SC20000	Traumatic epilepsy
37644	F132100	Progressive myoclonic epilepsy

Definition of variables

Lists of Medcodes and corresponding Read codes used for each variable can be found in Supplemental file 2. An initial list of Read codes was created for each variable, either based on previous research or by searching specific words in a Read code browser. Medcodes were matched to the Read code list using the CPRD Medical Dictionary. An additional search of the Medcodes was conducted to ensure all appropriate codes were used. Medcodes were used during the analysis in STATA as these are numeric codes. For variables using medication data, lists of prodcodes were generated by searching the CPRD product code list, which lists prodcodes against British National Formulary (BNF) information.

- **Age**: For cases: age = year of death – year of birth. For matched controls: age = year of death of the matched case – year of birth.

For epilepsy related factors (ie. Relating to seizures and treatment) and lifestyle factors, data from the CPRD was used from the date of death of the matched case up to 12 months prior. These variables are listed below:

- **Emergency department visit or emergency admission**: Emergency admissions or visits to emergency centres were identified from "Clinical data" from CPRD. These included keywords: seen by emergency clinician, in accident and emergency, emergency admission. A full list is available in Supplemental File 2.

- **Number of antiepileptic drugs (AEDs)**: Number of different types of AEDs prescribed in 12 months were grouped into categories: 0, 1, 2, 3 and "4 or more". Product codes ("Prodcode") were used from "Therapy data" to identify AEDs in the CPRD. A full list of Prodcodes and corresponding definitions is available in Supplemental File 2.

- **Status epilepticus**: recorded status epilepticus code in previous 12 months (medcode: 4093; readcode: F253.11) clinical CPRD data.[1]

- **Depression**: the variable was coded as either a documented diagnostic medcode related to "depression" from "Clinical data" or a prescription of antidepressants from "Therapy data" in the previous 12 months.[1] Antidepressants were identified through their product codes (prodcode) from therapy data. A list of medcodes for depression and prodcodes for antidepressants can be found in Supplemental File 2.

- **Smoking status**: Data was coded from medcodes related to smoking or smoking cessation interventions from "Clinical data" and overall smoking status if available in the CPRD "Additional Files". For any patients that did not have a smoking status recording in the 12-month data period, the last known recording from clinical data was used, as previously described by Booth et al.[2] The list of medcodes and readcodes used to identify smoking status can be found in Supplemental File 2.

- **Injury**: any injury documented in "Clinical data" was used. A list of medcodes from clinical CPRD data included: injuries, fractures, dislocations, burns, bruising, contusions, lacerations, abrasions, concussions and wounds.[1] A full list of medcodes and corresponding Read codes can be found in Supplemental File 2.

- **Seizure freedom**: recoded seizure freedom for > 12 months (medcode: 11015; readcode: 667F.00) in "Clinical data" from CPRD.[1]

For co-morbidity, data coded for patient's lifetime (within start and end dates with acceptable quality data recording):

- **Dementia**: code list included any medcodes for "dementia" and "Alzheimer's" in patient history from "Clinical data" in the CPRD. The list of medcodes and corresponding Read codes can be found in Supplemental File 2.

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- **Stroke**: code list included stroke, cerebral ischemia/arterial occlusion/haemorrhage/infarction. embolism in patient history from "Clinical data" in the CPRD. The list of medcodes and corresponding Read codes can be found in Supplemental File 2.

Table S2. Main cause of death of PWE registered in the CPRD between 2005 – 2013 by year

ICD-10 category (ICD-10 code)	2005 (%)	2006 (%)	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)
Epilepsy (G40-G41)	6.3	6.3	5.9	6.1	5.7	6.2	5.2	7.1	5.2
Certain infectious and parasitic diseases (A00-B99)	1.0	1.6	1.1	1.0	0.7	0.9	0.5	1.2	0.5
Neoplasms (C00-D48)	20.9	19.4	17.6	19.6	19.0	18.1	21.8	21.4	20.9
Diseases of the blood and blood-forming organs (D50-D89)	0.6	0.0	0.4	0.3	0.1	0.0	0.2	0.3	0.3
Endocrine, nutritional and metabolic diseases (E00-E90)	1.5	1.7	1.7	1.1	1.6	1.7	1.1	1.0	1.1
Mental and behavioural disorders (F00-F99)	4.6	3.8	5.8	5.0	6.6	4.5	10.7	10.9	10.5
Diseases of the nervous system (G00-G37, G43-G99)	4.6	5.1	5.1	6.0	7.5	5.5	7.3	5.6	7.2
Diseases of the circulatory system (I00-I99)	33.8	35.1	34.0	34.0	31.3	33.1	28.3	26.8	28.1
Diseases of the respiratory system (J00-J99)	12.9	16.3	14.7	13.6	13.0	14.5	12.6	12.7	12.5
Diseases of the digestive system (K00-KK93)	3.8	3.3	4.3	4.6	4.1	4.8	4.9	4.9	5.0
Diseases of the skin and subcutaneous tissue (L00-L99)	0.0	0.1	0.5	0.3	0.4	0.3	0.1	0.0	0.1
Diseases of the musculoskeletal system and connective tissue (M00-M99)	0.4	0.0	0.8	0.3	1.2	0.2	0.7	0.4	0.8
Diseases of the genitourinary system (N00-N99)	2.9	2.5	2.4	1.8	2.8	3.1	0.7	2.1	1.2
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	1.5	1.5	1.1	1.5	1.6	0.9	0.8	0.8	1.1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	1.5	1.3	1.8	1.7	1.0	2.3	1.7	1.8	1.0
External causes of morbidity and mortality (V01-X59, X85-Y98)	3.3	1.6	2.6	2.8	3.1	3.1	3.2	2.6	3.5
External causes of morbidity and mortality (intentional) (X60-X84)	0.4	0.4	0.1	0.4	0.4	0.8	0.2	0.3	1.0
Total (n)	521	687	761	785	836	874	886	956	987

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