A national study of epilepsy-related deaths in Scotland

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FULL-LENGTH ORIGINAL RESEARCH

A national study of epilepsy-related deaths in Scotland: Trends, mechanisms, and avoidable deaths

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Abstract

Objective: This study was undertaken to investigate the trends and mechanisms of epilepsy-related deaths in Scotland, highlighting the proportion that were potentially avoidable.

Methods: This was a retrospective observational data-linkage study of administrative data from 2009–2016. We linked nationwide data encompassing mortality records, hospital admissions, outpatient attendance, antiepileptic drug (AED) prescriptions, and regional primary care attendances. Adults (aged ≥16 years) suffering epilepsy-related death were identified for study using International Classification of Diseases, 10th Revision coding combined with AED prescriptions. We reported epilepsy-related mortality rate (MR), age-specific mortality ratios, multiple cause-of-death frequencies, and the proportion of potentially avoidable deaths (identified as those with an underlying cause listed as avoidable by the Office for National Statistics).

Results: A total of 1921 epilepsy-related deaths were identified across Scotland; 1185 (62%) decedents were hospitalized for seizures in the years leading up to death, yet only 518 (27%) were seen in a neurology clinic during the same period. MR remained unchanged over time, ranging from 5.9 to 8.7 per 100 000 Scottish population (95% confidence interval [CI] = −.05 to .66 per 100 000 for annual change in MR). Mortality ratios were significantly increased in young adults aged 16–54 years (2.3, 95% CI = 1.8–2.8), peaking at age 16–24 years (5.3, 95% CI = 1.8–8.8). Sudden unexpected death in epilepsy (SUDEP) constituted 30% of the 553 young adult epilepsy-related deaths, with several other non-SUDEP fatal mechanisms identified including aspiration pneumonia, cardiac arrest, AED or narcotic poisoning, drowning, and alcohol dependence. Seventy-six percent of young adult epilepsy-related deaths were potentially avoidable.

Significance: Epilepsy-related deaths are a major public health problem in Scotland, given that they are not reducing, people are dying young, and many deaths are potentially avoidable. SUDEP is only one of several important mechanisms by which epilepsy-related deaths are occurring in young adults. Services

may need to be re-evaluated to improve specialist referral following seizure-related hospital admissions.

KEYWORDS
cause of death, death certificates, mortality, routine data, terminal illness

1 | INTRODUCTION

Epilepsy is common and contributes to .7% of the global burden of diseases.[1] Of the 600 000 people with epilepsy (PWE) in the UK, 60 000 live in Scotland.[2] Although it is not often discussed with patients,[3,4] epilepsy is associated with significantly increased risk of premature death.[5] Some of those deaths may be unrelated to epilepsy. However, a substantial proportion relate to epilepsy itself, its treatment, or comorbidities worsened by epilepsy.[5,6] Together, these are termed "epilepsy-related deaths," and they are likely to contribute a significant burden of total years of potential life lost.[5,6] A nationwide study quantifying epilepsy-related deaths is yet to be undertaken in Scotland.[5] From a public health perspective, this is a pressing issue, as Scotland has a lower life expectancy than the rest of the UK and Western Europe.[7] It also has a larger proportion of its population living in rural and remote communities compared with the rest of the UK.[7] This inevitably presents challenges in epilepsy health care provision.[8]

More generally, the exact mechanisms by which epilepsy-related deaths occur remain unclear,[5,6] often making it difficult for clinicians to have a broad discussion about these with patients.[3,4] A recently proposed classification system for epilepsy-related deaths suggests these should include deaths occurring directly due to epilepsy (including sudden unexpected deaths in epilepsy [SUDEP] and seizure-related accidents), deaths occurring due to acute symptomatic seizures that would likely have gone on to become epilepsy (including after stroke or traumatic brain injury), deaths indirectly occurring due to epilepsy (including aspiration pneumonia or suicide), and deaths occurring due to the underlying etiology of epilepsy (including brain tumors and genetic conditions).[6] A way to test for the presence of all of these mechanisms in real-world data is to conduct a multiple cause of death (MCOD) analysis on deaths involving epilepsy.[9,10] To our knowledge, this has yet to be undertaken.[5] Traditionally, cause of death statistics are derived from the underlying cause of death on a death certificate only.[9–11] This is defined as the disease or condition that initiated the chain of morbidities and mechanisms that lead directly to death.[10] MCOD analysis differs by including not only the underlying cause of death, but also all of the other causes of death listed as contributory morbidities and mechanisms in the death certificate.[9,11] Reporting MCOD data, advocated by the World Health Organization, would allow a more complete clinical picture to be drawn of all of the mechanisms implicated in epilepsy-related deaths.[9–11]

Key Points

- Epilepsy-related deaths remain common in Scotland, and have failed to reduce over time
- A substantial percentage of epilepsy-related hospital admissions do not lead to outpatient neurology care
- The risk of epilepsy-related death is significantly increased in young adults aged 16–54 years
- SUDEP may constitute 30% of young adult epilepsy-related deaths
- As many as 80% of young adult epilepsy-related deaths may be avoidable

It is thought many epilepsy-related deaths may be avoidable,[12–14] although this is yet to be quantified.[5] The Office for National Statistics (ONS) has recently produced a list of underlying causes of death that should not, or should only infrequently, have given rise to death in the presence of timely and effective health care or public health policies.[15] This Revised Definition of Avoidable Mortality list (RDAM 2016) is based on research from Nolte and McKee[16] and Page et al.,[17] and has been refined through public consultation with multiple organizations, including the UK government, academics, and charities.[15] The list identifies conditions for which there are effective public health and primary prevention strategies before the onset of disease (e.g., immunization) to reduce the incidence of death, or conditions for which, after the onset of disease, effective treatments are available to reduce case fatality.[18] For most causes, there is an upper age limit of 74 years.[15] RDAM 2016 is used by the UK government and the Department of Health and Social Care to determine progress in reducing the prevalence of preventable ill health and premature death, and the gap between local authorities.[18] In Scotland, a seminal paper in *The Lancet* evaluated nationwide health system performance through 2001–2013 using RDAM 2016 to illustrate

that during the 50.5 million person-years of study, there had been 166 245 potentially avoidable deaths.[8] Although a specific condition can be considered avoidable, this does not mean that every death from that condition could be averted. Instead, this measure is designed to highlight areas of potential weaknesses in health care that could benefit from further in-depth investigation.[18]

We report the first national study of epilepsy-related deaths in Scotland. We aimed to first establish the total number of epilepsy-related deaths in the country, whether these have changed over time, and how they compare to risk of mortality in the general population by age. We then aimed to describe all of the mechanisms by which epilepsy-related deaths had occurred in the age groups at increased risk (using MCOD data), and to estimate what proportion of these deaths were potentially avoidable (using the RDAM 2016 list).

2 | MATERIALS AND METHODS

2.1 | Setting

All individuals accessing health care in Scotland are provided with a unique identification number (the Community Health Index [CHI] number). This can, therefore, be used to create nationally linked research datasets derived from the entire Scottish population.[8] All deaths are registered centrally at the National Records of Scotland (NRS) within 8 days of occurrence (approximately 55 000 annually).[19] The free-text causes of death listed on death certificates are coded by NRS into their corresponding International Classification of Diseases, 10th Revision (ICD-10) codes.[19] There is a world-leading mortality review system in place in Scotland in which these causes of death are routinely scrutinized for accuracy and amended where necessary (summarized in Figure S1).[20,21] Deaths in which a cause cannot be immediately identified because they are sudden, suspicious, accidental, or unexplained are reported to a statutory legal official (the Procurator Fiscal).[22] The Procurator Fiscal reviews the history and circumstances of death and either accepts the cause if satisfied it was natural, or arranges an autopsy. Suspected SUDEP would normally proceed to autopsy in Scotland.[23]

2.2 | Study design, data sources, and participants

This was a national administrative data linkage study. Using CHI numbers, Scotland-wide person-level data were retrospectively linked over 7 consecutive years (January 1, 2009–January 1, 2016) to identify all of the epilepsy-related deaths in adults (aged ≥16 years) during this period. We first linked NRS death records[19] to Prescribing Information System (PIS) Scottish prescribing data.[24] PIS is a mandatory national prescribing dataset used to track the community drug history of the entire Scottish population to facilitate public drug reimbursement.[24] Epilepsy-related deaths were defined as those in which death had occurred with at least one ICD-10-coded cause listed as G40 (epilepsy), G41 (status epilepticus), or R56.8 (seizures) in any position within the NRS cause of death record, combined with a requirement for such individuals to have also had at least one community-prescribed antiepileptic drug (AED) in their PIS dataset. This combined NRS and PIS algorithm demonstrated a high positive predictive value of 91% (95% confidence interval [CI] = 89%–94%) and a high sensitivity of 81% (95% CI = 77%–84%) for correctly identifying a diagnosis of epilepsy.[25,26] It was also consistent with national guidance that the presence of an epilepsy code anywhere in the cause of death record indicates that epilepsy was thought by the certifying doctor to be either part of the sequence of events leading to death or else a factor contributing to the death.[10,27] Data on autopsy status (performed or not), place of death, sex, and Scottish Index of Multiple Deprivation (SIMD) quintiles were automatically uploaded from NRS.[19,28,29]

2.3 | Enrichment linking

We enriched the NRS and PIS data by linking it to nationwide hospital admissions[30] and outpatient attendance data,[31] as well as to regional primary care data (see Table 1).[28]

2.4 | Variables and data sources

2.4.1 | Identifying the mechanisms of epilepsy-related death using MCOD data

We created a MCOD dataset by pooling together all of the ICD-10-coded causes of death listed alongside G40–G41/R56.8 in the NRS dataset.[9,10] As there is no specific ICD-10 code for SUDEP,[32] we captured SUDEP from the free-text causes of death section of the NRS records, where SUDEP deaths were identified as those with "sudden unexplained/unexpected death in epilepsy" listed in the free-text cause of death section. We identified *definite* SUDEP as those cases in which autopsy was performed, and *probable* SUDEP as those without autopsy.[33] Given our access to MCOD data, we were able to identify SUDEP *Plus* as those with an additional condition or conditions listed as a cause of death alongside SUDEP.[33] These definitions were

TABLE 1 Case ascertainment

Identification of epilepsy-related deaths = A + B

A. *NRS death records*.[19] Those who had died with ≥1 G40–G41 ICD-10 code (epilepsy and status epilepticus) and/or R56.8 (seizures) listed within their causes of death.

B. *AEDs on the Scottish PIS*.[24] Those who were prescribed ≥1 AED (regardless of their cause of death).

Enrichment linking = A + B ± C and/or D ± E

C. *SMR01 hospital admissions*.[30] Those who had experienced ≥1 hospital admission diagnosis coded as G40–G41 and/or R56.8, regardless of their cause of death. SMR01 is a mandatory national dataset capturing all of the inpatient hospital admissions in Scotland; 1.4 million SMR01 records are generated annually.[30] Data collected include a mandatory diagnostic field containing up to six ICD-10-coded hospital admission diagnoses.[30]

D. *Primary care*. Those who had ≥1 epilepsy-related (Read code F25) primary care attendance (regardless of cause of death). Read codes are a coded thesaurus of clinical terms used in primary care to create electronic health records. GPs use Vision medical software to build EHRs for patients in primary care. Within this system, GPs record symptoms, diagnoses, and prescriptions using Read codes.[44] This makes it possible to track diagnostic primary care NHS data within a data linkage study environment. As there is no routine primary care epilepsy dataset available in Scotland currently, we established one by putting together a convenience sample of 10% of all 900 Scottish GPs using methods published in detail previously (Appendix S2).[26] We extracted all other coded diseases and activities occurring in the F25 patients to gain insight into the burden of comorbidity from mental health problems (including depression, psychiatric illness, and suicidality), learning disabilities, congenital abnormalities, and substance misuse (including alcohol and drug abuse). Additionally, for primary care data, we were able to estimate a duration of epilepsy as the time between the first ever F25 code and the date of death (see Appendices S3 and S4 for the full list of Read codes used). The baseline characteristics of those with primary care data were compared to the rest of the group to assess their representativeness. For the categorical baseline characteristics, comparison was made using a chi-squared independence test alongside post hoc *z*-tests for independent proportions, applied with Bonferroni correction. For continuous variables, an independent samples *t*-test was used. A two-sided 5% significance cutoff was used throughout.

E. *SMR00 outpatient attendance*. We linked participants to their SMR00 dataset to flag which had attended a neurology clinic during the study period. SMR00 is a national outpatient activity dataset in which it is mandatory to record whether patients attended clinic and under which speciality/discipline, allowing hospitals to be reimbursed for providing clinic services.[31] Neurology clinic attendances are coded as AH (AH1 = patient was seen, AH5 = patient attended but was not seen [could not wait], AH8 = patient did not attend).[31] This makes it possible for us to track whether deceased patients had previously attended neurology clinics anywhere in the country during the study period. We excluded the outpatient diagnosis field, as this is poorly recorded due to being optional.[31]

Abbreviations: AED, antiepileptic drug; EHR, electronic health record; GP, general practice; ICD-10, International Classification of Diseases, 10th Revision; NHS, National Health Service; NRS, National Records of Scotland; PIS, Prescribing Information System; SMR, Scottish Morbidity Record.

consistent with the Nashef 2012 classification of definite SUDEP, probable SUDEP, and SUDEP Plus.[33]

2.4.2 | Identifying potentially avoidable epilepsy-related deaths

Table 2 lists the underlying causes of death used by the ONS to indicate a potentially avoidable death in RDAM 2016.[8,15] Consequently, we identified the potentially avoidable epilepsy-related deaths as any in which the underlying cause of death was in this RDAM 2016 list.[8,34]

2.5 | Bias and study size

Selection bias was reduced by examining data from the entire Scottish population,[8,19,24,30] which also maximized the sample size for observation. Misclassification bias was reduced by using the optimal case-ascertainment codes identified during prior validation,[25,26] cause of death records with a central quality assurance process in place,[20,21] and an established list of ICD-10 codes produced by the ONS for identifying potentially avoidable mortality.[8,15,34]

2.6 | Statistical analysis

2.6.1 | Mortality rates and ratios

We reported the total number of epilepsy-related deaths in the study period. We calculated direct age-standardized mortality rate (MR) per 100 000 Scottish population each year using the 2013 European Standard Population distributed into the age groups 16–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years, and 75+ years (formulae in Appendix S1a).[35] We used a linear regression model of epilepsy-related MR plotted over time to assess for significant change (indicated by annual change in MR [ΔMR] with a 95% CI not crossing 0). To

compare epilepsy-related mortality to mortality in the general Scottish population, we used an indirect method to estimate age-specific mortality ratios for the age groups listed above (detailed in Appendix S1b).[35] Annual change in mortality ratios was assessed using linear regression. Primary analysis looked at the MR and mortality ratios in the overall population. A subgroup analysis was reported by sex.

2.6.2 | MCOD data

MCOD analysis was conducted for the age groups in which standardized mortality ratio (SMR) was significantly increased. The deaths were split into SUDEP and non-SUDEP epilepsy-related deaths. We reported the total number of SUDEP cases, identifying what proportion were definite SUDEP, probable SUDEP, and SUDEP Plus.[33] For the non-SUDEP deaths, we counted the number of times each individual ICD-10 code and chapter group was listed as a cause of death, listing each chapter frequency as a percentage of the total code frequency.[36]

2.6.3 | Potentially avoidable deaths

We reported the total number of potentially avoidable epilepsy-related deaths and grouped these according to the RDAM 2016 disease groups to which they belonged (Table 2),[8,15] reporting these as percentages of the total number affected.

Data were processed using RStudio version 1.2.1335. Ninety-five percent CIs were listed, where relevant, including using exact binomial tests for proportional estimates. Categories with less than five events/participants were combined or reported as "<5" to avoid patient identification.

2.7 | Approvals

This study was approved by South East Scotland Research Ethics Committee 2 (15/SS/0165, IRAS 181131) and the Scottish Public Benefit and Privacy Panel for Health and Social Care.

3 | RESULTS

3.1 | Frequency and demographics of epilepsy-related deaths

A total of 1921 epilepsy-related deaths were identified across Scotland through 2009–2016 (Figure 1). This was from nationwide NRS and PIS data combined using the validated algorithm ≥1 G40–G41 and/or R56.8 cause of death coded in NRS + ≥1 community-prescribed AED in PIS.[26]

Baseline characteristics of the 1921 people are summarized in Table 3. The deaths mostly occurred in the largest four Scottish Health Board regions, at a median age of 67 years (range = 16–101 years), with 53% of the 1921 deaths occurring in men. Most deaths occurred in an National Health Service (NHS) hospital (47% of the 1921 deaths) or at home (29% of the 1921 deaths), and the majority had lived in more deprived areas of Scotland (Figure S2).[29] Although 1185 of 1921 people who went on to suffer an epilepsy-related death had experienced at least one seizure- or epilepsy-related hospital admission during the study period (i.e., 62%), only 518 of 1921 had been seen in a neurology clinic during that same period (i.e., 27%). Of the 518 seen in a neurology clinic, 360 were from the 1185 with at least one seizure- or epilepsy-related hospital admission (i.e., 30% of the 1185 people).

3.2 | Annual trend in epilepsy-related death MR

Figure 2A is a linear regression plot of annual age-standardized epilepsy-related MR per 100 000 Scottish population.[35] The overall MR ranged between 5.9 and 8.7/100 000 during the study period, demonstrating no significant change over time (95% CI = −.05 to .66/100 000 for annual ΔMR; calculated in Appendix S5a). In men, MR ranged between 6.6 and 10.1/100 000 men, demonstrating no significant change over time (95% CI = −.19 to .80/100 000 for annual ΔMR; Appendix S5b). In women, it ranged between 5.2 and 7.3/100 0000 women, also demonstrating no significant change over time (95% CI = −.009 to .544/100 000 for annual ΔMR, Appendix S5c). Although there was a tendency for MRs to be slightly higher in men than women, overlap of the CIs meant that these differences were generally not significant (Figure S3).

3.3 | Trend in age-specific mortality ratios

Figure 2B–H is a panel of linear regression plots for age-specific mortality ratios for epilepsy-related deaths each year. These increased significantly over the study period for those aged 55–64 years (95% CI = .00065–.19 for annual change in mortality ratio), but otherwise remained unchanged in all remaining age group strata (calculated in Appendix S5d). Trends in age-specific mortality ratios were similar between men and women (Figure S4 and Appendix S5e–f).

TABLE 2 Potentially avoidable causes of death according to the Office for National Statistics Revised Definition of Avoidable Mortality 2016 classification

Potentially avoidable underlying cause of death; ICD-10 codes	Number of young adult epilepsy-related deaths affected (% of total, 95% CI)
Neurological disorders	
Epilepsy and status epilepticus; G40–G41	294 (69.8%, 65.2%–74.2%)
Cardiovascular diseases	
Rheumatic and other valvular heart disease; I01–I09	34 (8.1%, 5.7%–11.1%)
Hypertensive diseases; I10–I15	
Ischemic heart disease; I20–I25	
DVT with pulmonary embolism; I26, I80.1–I80.3, I80.9, I82.9	
Cerebrovascular diseases; I60–I69	
Aortic aneurysm and dissection; I71	
Drug use disorders	
Alcohol related diseases, excluding external causes; F10, G31.2, G62.1, I42.6, K29.2, K70, K73, K74 (excluding K74.3–K74.5), K86.0	28 (6.7%, 4.5%–9.5%)
Illicit drug use disorders; F11–F16, F18–F19	
Neoplasms	
Malignant neoplasm of lip, oral cavity, and pharynx; C00–C14	13 (3.1%, 1.7%–5.2%)
Malignant neoplasm of esophagus; C15	
Malignant neoplasm of stomach; C16	
Malignant neoplasm of colon and rectum; C18–C21	
Malignant neoplasm of liver; C22	
Malignant neoplasm of trachea, bronchus, and lung; C33–C34	
Malignant melanoma of skin; C43	
Mesothelioma; C45	
Malignant neoplasm of breast; C50	
Malignant neoplasm of cervix uteri; C53	
Malignant neoplasm of bladder; C67	
Malignant neoplasm of thyroid gland; C73	
Hodgkin disease; C81	
Leukemia; C91, C92.0	
Malignant neoplasm of testis; C62	
Malignant neoplasm of unspecified parts of uterus and body of uterus; C54–C55	
Benign neoplasms; D10–D36	
Respiratory diseases	
Influenza (including swine flu); J09–J11	11 (2.6%, 1.3%–4.6%)
Pneumonia; J12–J18	
Chronic obstructive pulmonary disorder; J40–J44	
Asthma; J45–J46	
Selected respiratory diseases; J00–J06, J20–J22, J30–J39	
Maternal and infant	
Complications of perinatal period; P00–P96, A33	11 (2.6%, 1.3%–4.6%)
Congenital malformations of the circulatory system; Q20–Q28	
Spina bifida; Q05	

(Continues)

TABLE 2 (Continued)

Potentially avoidable underlying cause of death; ICD-10 codes	Number of young adult epilepsy-related deaths affected (% of total, 95% CI)
Unintentional injuries	
Transport accidents; V01–V99	9 (2.1%, 1.0%–4.0%)
Accidental injury; W00–X59	
Nutritional, endocrine, and metabolic	
Diabetes mellitus; E10–E14	8 (1.9%, .8%–3.7%)
Diseases of the thyroid; E00–E07	
Addison disease; E27.1	
Digestive disorders	
Gastric and duodenal ulcer; K25–K28	
Acute abdomen, appendicitis, intestinal obstruction, cholecystitis/lithiasis, pancreatitis, hernia; K35–K38, K40–K46, K80–K83, K85, K86.1–K86.9, K91.5	
Genitourinary disorders	
Nephritis and nephrosis; N00–N07, N17–N19, N25–N27	
Obstructive uropathy and prostatic hyperplasia; N13, N20–N21, N35, N40, N99.1	
Intentional injuries	
Suicide and self-inflicted injuries; X60–X84, Y10–Y34	8 (1.9%, .8%–3.7%)
Homicide/assault; X85–Y09, U50.9	
Misadventures to patients during surgical and medical care; Y60–Y69, Y83, Y84	
Infections	
Tuberculosis; A15–A19, B90	5 (1.2%, .4%–2.7%)
Selected invasive bacterial and protozoal infections; A38–A41, A46, A48.1, B50–B54, G00, G03, J02, L03	
Hepatitis C; B17.1, B18.2	
Pertussis (whooping cough); A37	
Measles; B05	
Rubella; B06	
Other infections (diphtheria, tetanus, poliomyelitis, and varicella); A35, A36, A80, B01	
Intestinal infections; A00–A09	
HIV/AIDS; B20–B24	
Total	421

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; DVT, deep venous thrombosis; HIV, human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th Revision.

Table 4 summarizes the mean age-specific mortality ratios for epilepsy-related deaths throughout the study period, demonstrating that these were significantly more common in young adults aged 16–54 years, peaking at 5.3 (95% CI = 1.8–8.8) in the age group 16–24 years, followed by 3.6 (95% CI = 1.8–5.4) in the age group 25–34 years. The mean overall mortality ratio for age 16–54 years remained significantly raised at 2.3 (95% CI = 1.8–2.8), and was lower than in the general population in those aged ≥55 years (.52, 95% CI = .45–.60).

3.4 | Mechanisms involved with epilepsy-related death

Epilepsy-related deaths were significantly increased in young adults aged 16–54 years, occurring in 553 of these participants. Three hundred forty-nine of 553 were male (i.e., 63%). Sixty-two of 553 (i.e., 11%) had primary care Read code data available. Mean age in those with primary care data was 40.2 years (±11.3 years SD). This was no different from a mean age of 39.7 years (±10.5 years SD)

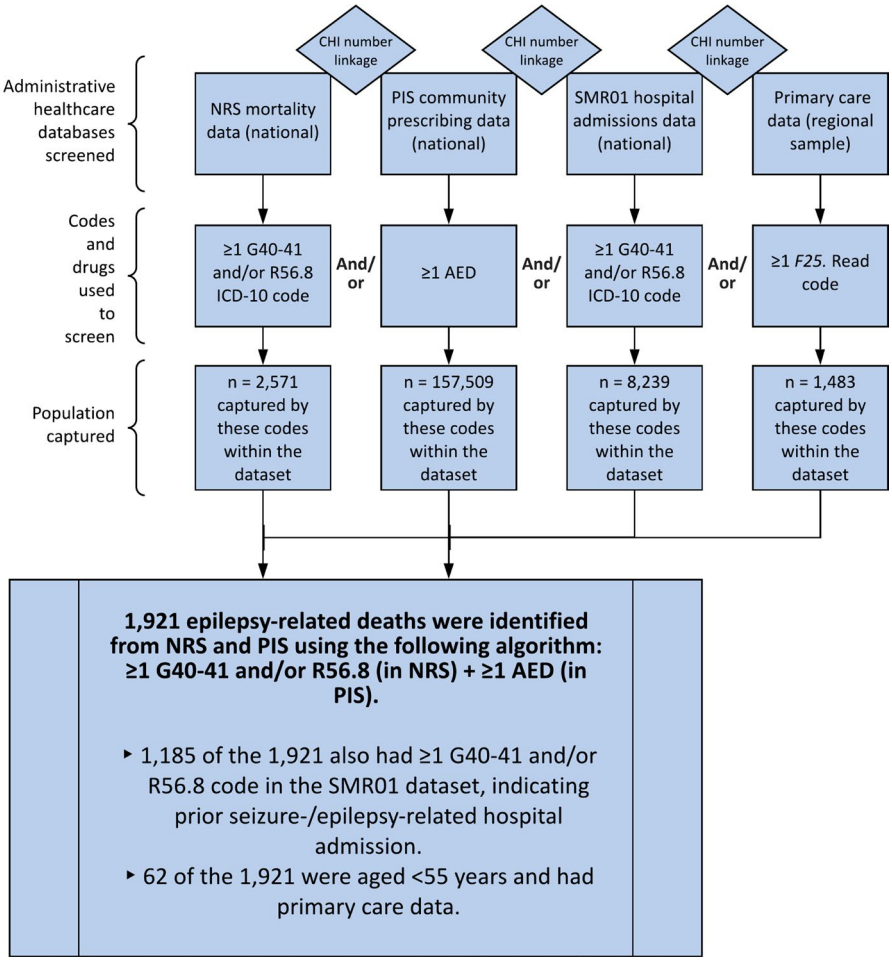

FIGURE 1 Data linkage and participant flow diagram. The datasets were linked using Community Health Index (CHI) numbers (unique patient identification numbers) by Electronic Data Research and Innovation Service (eDRIS), based at the Farr Institute, Scotland. The linked data were then made available to us as a deidentified research dataset in a secure analytical platform (a data safe haven).[28] eDRIS removed 11 people (<1%) and 420 people (5%) from the National Records of Scotland (NRS) and Scottish Morbidity Record 01 (SMR01) data files, respectively, as they had no CHI number, precluding linkage. Linkage was otherwise complete, and a large dataset containing information from 159 032 deceased adults across Scotland was created.[26] AED, antiepileptic drug; *F25*, primary care diagnostic Read codes for epilepsy; G40–G41, International Classification of Diseases, 10th Revision (ICD-10) codes for epilepsy and status epilepticus; PIS, Prescribing Information System; R56.8, ICD-10 code for seizures

in the remaining 491 young adults without primary care data ($p = .74$). The proportions of men and women were also the same in both groups ($p = .60$). There was also no difference in proportions living in each SIMD quintile area of deprivation between both groups ($p = .63$), proportion with previous epilepsy-related hospital admission ($p = .63$), and proportion previously seen in a neurology clinic ($p = .97$; see Table S1. The primary care data revealed a median epilepsy duration of 17 years (range = 1–55 years). There were Read code indicators of comorbid mental health problems in 50% of the 62 participants, alcohol and drug abuse in 44% of the 62 participants, and learning disabilities or congenital malformations in 39% of the 62 participants.

Of 553 young adult epilepsy-related deaths, 166 were SUDEP (i.e., 30%). One hundred sixty-five of 166 SUDEP cases underwent investigation by the Procurator Fiscal (i.e., 99%). One hundred forty-nine of 166 cases (i.e., 90%) underwent autopsy and were regarded as definite SUDEP.[33] The remaining 17 of 166 cases (i.e., 10%) did not have an autopsy and were regarded as probable SUDEP.[33] An additional cause of death was listed alongside SUDEP in 30 of 166 SUDEP cases (i.e., 18%); these were regarded as SUDEP Plus.[33] Twenty-three of 30 SUDEP Plus cases (i.e., 77%) underwent autopsy. One hundred seven of 166 SUDEP cases were male (i.e., 64%). One hundred forty-four of 166 SUDEP cases occurred at home (i.e., 87%), with the remaining small minority occurring in an NHS

TABLE 3 Characteristics of epilepsy-related death population

Scottish NHS Health Board, NRS data	Total number of epilepsy-related deaths, 2009–2016	Average yearly general Scottish population size, 2009–2016
NHS Greater Glasgow & Clyde	451	956 927
NHS Lanarkshire	259	536 332
NHS Lothian	254	721 051
NHS Grampian	198	488 611
NHS Aryshire & Arran	155	308 405
NHS Tayside	144	346 970
NHS Fife	137	303 999
NHS Forth Valley	116	249 793
NHS Highland	112	267 752
NHS Dumfries & Galloway	48	125 994
NHS Borders	33	95 055
NHS Orkney, NHS Shetland, & NHS Western Isles	14	40 903
Total	1921 (1010 male)	
Median age at death, NRS data, years	67 (range = 16–101)	
Place of death, NRS data	Total	Proportion (95% CI)
NHS hospital	898	46.7% (44.5%–49.0%)
Noninstitutional, e.g., at home	562	29.3% (27.2%–31.3%)
Private nursing home/private hospital	377	19.6% (17.9%–21.5%)
Home for the elderly	57	3.0% (2.3%–3.8%)
Miscellaneous (GP surgery, clinic, prison, contractual hospital, other home)	27	1.4% (.9%–2.0%)
Cause of death enquiries, NRS data		
Medical enquiry into cause of death	189	9.8% (8.5%–11.3%)
Procurator Fiscal input to cause of death	466	24.3% (22.4%–26.2%)
Autopsy input to cause of death	356	18.5% (16.8%–20.3%)
Clinical care indicators, linked SMR01, SMR00, PIS data		
Seen in neurology clinic ≥once during 2009–2016 (≥1 AH1 code in SMR00)	518	27.0% (25.0%–29.0%)
≥1 seizure-/epilepsy-related hospital admission during 2009–2016 (≥1 G40–G41 and/or R56.8 code in SMR01)	1185	61.7% (59.5%–63.9%)
≥1 seizure-/epilepsy-related hospital admission during 2009–2016 (≥1 G40–G41 and/or R56.8 code in SMR01) and also seen in neurology clinic ≥once during 2009–2016 (≥1 AH1 code in SMR00)	360	

Abbreviations: AH1, patient was seen neurology clinic attendance; CI, confidence interval; G40–G41, ICD-10 codes for epilepsy; GP, general practice; ICD-10, International Classification of Diseases, 10th Revision; NHS, National Health Service; NRS, National Records of Scotland; PIS, Prescribing Information System; R56.8, ICD-10 code for seizure; SMR, Scottish Morbidity Record (01 = hospital admissions, 00 = outpatient clinic attendance).

hospital or other setting. Sixty-eight of 166 SUDEP cases (i.e., 41%) had experienced at least one seizure-related and/or epilepsy-related hospital admission during the study period. A similar number of 79 of 166 SUDEP cases (i.e., 48%) had been seen at least once in a neurology clinic during the same period. Sixty percent of the 166 SUDEP subjects had lived in the two most deprived SIMD quintile areas.[29]

Table 5 summarizes the MCOD data for the 387 young adult epilepsy-related deaths that were not SUDEP. In total, there were 1365 coded disease mechanisms underlying and contributing to death in this population. By definition, each of these individuals had to have at least one of these causes coded as G40–G41/R56.8.[9,10,27] These codes contributed 30% of the 1365 coded disease mechanisms. By far the most commonly used individual code

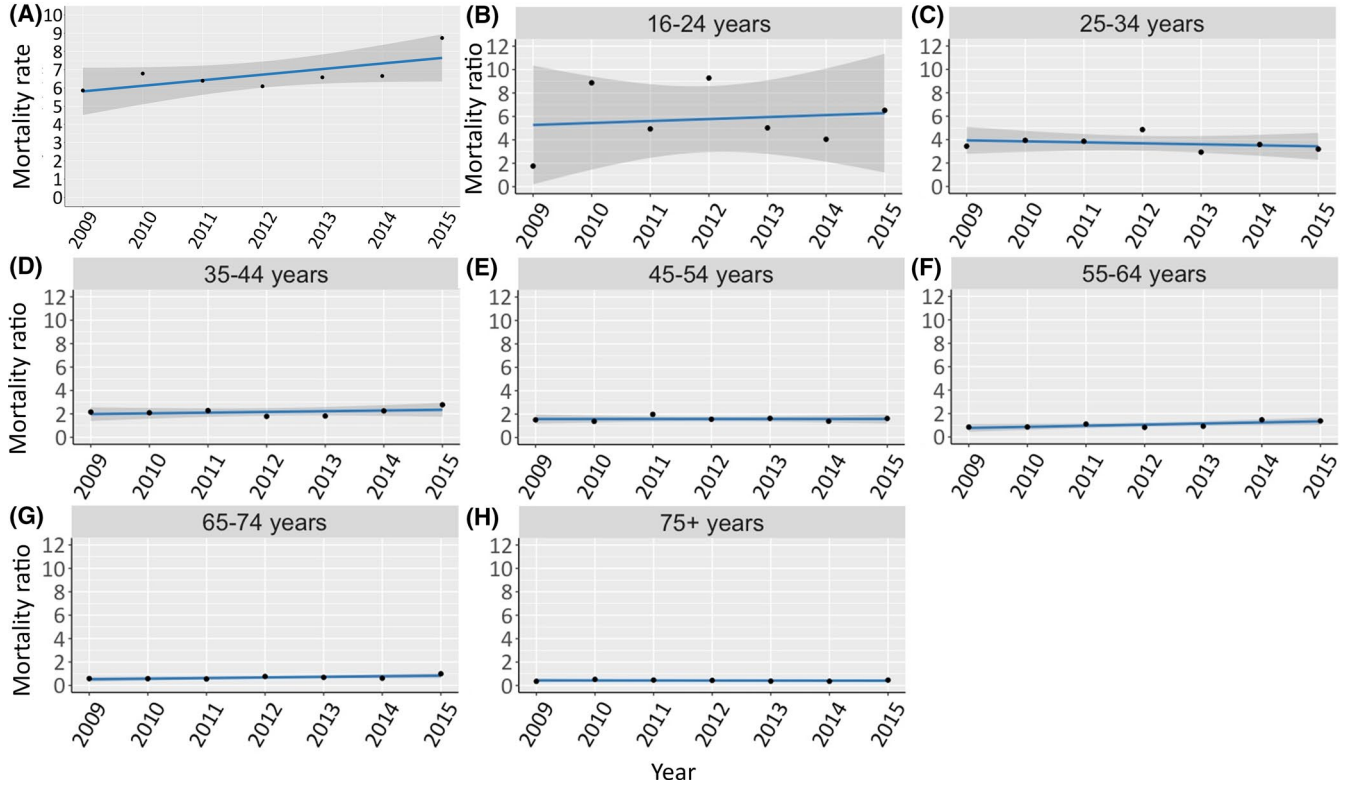

FIGURE 2 Linear regression plots of mortality rate (MR) and age-specific mortality ratios overall. Each dot plot is fitted with a linear regression line and confidence interval (gray shadow). (A) Direct age-standardized MR per 100 000 Scottish population each year. Figure illustrates little change in epilepsy-related mortality rate over time. (B–H) Annual age-specific mortality ratios for epilepsy-related death in each age group of study. These illustrate little change over time, with persistently increased estimates in those aged 16–54 years

TABLE 4 Comparative risks of epilepsy-related death

Age group	Mean national Scottish mortality rate per 100 000 population per year, 2009–2016	Mean size of the Scottish epilepsy population each year, 2009–2016	Expected mean number of deaths in the Scottish epilepsy population each year, 2009–2016	Observed mean number of epilepsy-related deaths per year in Scotland, 2009–2016 (study population)	Age-specific mortality ratio (95% CI)	
					By age group κ	Overall
16–24 years	45	3740	2	9	5.3 (1.8–8.8)	2.3 (1.8–2.8) in those aged 16–54 years
25–34 years	87	4908	4	16	3.6 (1.8–5.4)	
35–44 years	173	5408	9	20	2.2 (1.2–3.1)	
45–54 years	340	6324	21	34	1.6 (1.1–2.1)	
55–64 years	806	5126	41	43	1.0 (.7–1.4)	.52 (.45–.60) in those aged ≥55 years
65–74 years	2016	3927	79	54	.7 (.5–.9)	
75+ years	8142	2889	235	98	.4 (.3–.5)	

Abbreviation: CI, confidence interval.

within this group was G40.9 (epilepsy unspecified). R56.8 (seizures) and G41.9 (status epilepticus) were reported far less frequently. The five most common cause of death mechanisms to accompany epilepsy were J00–J99 diseases of the respiratory system (mainly aspiration pneumonia [J69.0]), I00–I99 diseases of the circulatory system (mainly cardiac arrest [I46.9]), G00–G37 and G42–G99 other nonepilepsy diseases of the nervous system (mainly cerebral palsy [G80.9]), S00–T98 injuries, poisoning, and other external causes (mainly AED poisoning [T42.6] or drowning [T75.1]), and F00–F99 deaths in relation to mental and behavioral disorders (mainly in relation to

alcohol dependence [F10.2]). The next most common were V01–Y98 external causes of morbidity and mortality (mainly narcotic poisoning [X42]), Q00–Q99 congenital malformations (mainly Down syndrome [Q90.9]), and K00–K93 diseases of the digestive system (mainly alcoholic liver disease [K70.9]). Fatal neoplasms were mainly of the brain (C71.9).

One hundred ninety-four of 387 non-SUDEP epilepsy-related deaths (i.e., 50%) underwent investigation by the Procurator Fiscal, indicating that they were likely to have been accidental, unexpected, unexplained, sudden, or suspicious. Of these 194 investigated cases, 106 underwent autopsy (i.e., 55%), and, following autopsy, SUDEP was not listed as a cause of death in each of the 106 cases. Table S2 summarizes MCOD data for these 106 cases. Alongside epilepsy and seizures, many of the deaths involved injury and poisoning (including AED or narcotic poisoning, and drowning). Table S3 summarizes MCOD data for the remaining 88 of 194 cases. Although a decision was made not to perform autopsy in these 88 cases, we undertook a post hoc "worst-case" scenario analysis in which we counted all of these 88 deaths as if they had been listed as SUDEP. This was done to help ensure we did not underestimate the overall burden of SUDEP in the study, as these 88 deaths were referred to the Procurator Fiscal but did not undergo autopsy. In this worst-case scenario, the number of SUDEP cases would increase to 254 from 166, constituting 45% of the 553 young adult epilepsy-related deaths instead of the original 30% reported.

3.5 | Potentially avoidable epilepsy-related deaths in the young adults

Four hundred twenty-one of 553 young adult epilepsy-related deaths (i.e., 76%) had an underlying cause in the RDAM 2016 list, indicating that these were potentially avoidable.[8,15] These deaths are summarized in Table 2, demonstrating that the most common reason for them being classified as potentially avoidable was having epilepsy itself (G40–G41) coded as the underlying cause of death (contributing 70% of the 421 potentially avoidable cases). Cardiovascular disease then alcohol and drug abuse were the next most common underlying mechanisms to contribute to the potentially avoidable cases.

4 | DISCUSSION

4.1 | Summary of findings

This study shows that epilepsy-related deaths remain common in Scotland. Despite a high number of epilepsy-related hospital admissions in the period leading up to death, there is relatively little outpatient neurology clinic input. Many of those experiencing epilepsy-related deaths live in Scotland's most deprived areas. The rate of epilepsy-related deaths has failed to reduce over time, and young adults appear to be at the highest risk. Although SUDEP is a common mechanism of death in this group, it is only one of many common mechanisms contributing to the burden of epilepsy-related death. There may be a large burden of potentially avoidable epilepsy-related deaths in young adults, as many as half of young adults experiencing epilepsy-related death may have had comorbid mental health problems, and alcohol or drug abuse may be present in 40%. Although the study findings are limited to 2009–2016, they remain relevant, as few new treatments or guidelines on epilepsy management have been implemented since this period.[1] This study helps provide a methodological framework for future national study of epilepsy-related mortality in Scotland and other countries with well-linked administrative health care datasets.

4.2 | Research in context

The study results complement the only other population-based study investigating mortality in PWE in Scotland.[37] This was limited to using only a regional cohort of PWE attending a specialist epilepsy service in one hospital in Glasgow between 1981 and 2001.[37] The study estimated SMRs of 1.42–2.05, identifying the greatest risk in those aged <30 years (SMR up to 7.03). These elevated risk figures are similar to those in our study, more than a decade after this study and now using data from the entire Scottish population. This suggests little has improved in Scottish epilepsy care despite those early regional warnings of increased premature mortality. More widely, the current study results also complement those of our recent systematic review of mortality in PWE, where a median SMR range of 2.2–3.4 was identified globally across 103 observational studies, with mortality in PWE failing to fall between 1950 and the present.[5]

The risk of epilepsy-related death in the current study peaked at age 16–24 years. This is a vulnerable period of transition from pediatric to adult care, and it may be that more needs to be done to support epilepsy transition services in Scotland. Whereas the literature often suggests mortality in PWE is increased largely for children and young adults aged <25 years due to congenital epilepsies,[13] we demonstrate that increased risk can persist well beyond this age group into the fifth decade, suggesting there may also be important acquired factors. Our primary care dataset indicates that some of these may be comorbid mental health problems, including depression,

TABLE 5 MCOD data in the non-SUDEP epilepsy-related death population of 387 cases

ICD-10 chapters	ICD-10-coded causes of death as chapters	Times a code from this chapter was used as a cause of death, *n* (% of total, 95% CI)	ICD-10-coded causes of death as individual codes within chapters	Times each individual code was used as a cause of death, *n*
VI, XVIII	G40–G41, R56.8: epilepsy, status epilepticus, and seizures	404 (29.6%, 27.2%–32.1%)	G40.9: epilepsy, unspecified	311
			R56.8: seizures	46
			G41.9: status epilepticus, unspecified	22
			G40.3: generalized idiopathic epilepsy and epileptic syndromes	8
			G40.5: special epileptic syndromes	6
			G40.6: grand mal seizures unspecified (with or without petit mal)	6
X	J00–J99: diseases of the respiratory system	159 (11.6%, 10.0%–13.5%)	J69.0: pneumonitis due to food and vomit	53
			J18.9: pneumonia, unspecified	35
			J18.0: bronchopneumonia, unspecified	24
			J98.8: other specified respiratory disorders	9
			J44.9: chronic obstructive pulmonary disease, unspecified	8
			J45.9: asthma, unspecified	7
			J22: unspecified acute lower respiratory infection	6
IX	I00–I99: diseases of the circulatory system	128 (9.4%, 7.9%–11.0%)	I46.9: cardiac arrest, unspecified	21
			I25.9: chronic ischemic heart disease, unspecified	15
			I25.1: atherosclerotic heart disease	10
			I64: stroke, not specified as hemorrhage or infarction	10
			I21.9: acute myocardial infarction, unspecified	9
			I26.9: pulmonary embolism without mention of acute cor pulmonale	5
			I51.7: cardiomegaly	5
VI	G00–G37, G42–G99: other diseases of the nervous system	102 (7.5%, 6.1%–9.0%)	G80.9: cerebral palsy, unspecified	36
			G93.1: anoxic brain damage not elsewhere classified	19
			G35: multiple sclerosis	9
			G30.9: Alzheimer disease, unspecified	8
			G80.8: other cerebral palsy	5

(Continues)

TABLE 5 (Continued)

ICD-10 chapters	ICD-10-coded causes of death as chapters	Times a code from this chapter was used as a cause of death, *n* (% of total, 95% CI)	ICD-10-coded causes of death as individual codes within chapters	Times each individual code was used as a cause of death, *n*
XIX	S00–T98: injuries, poisoning, and certain other consequences of external causes	101 (7.4%, 6.1%–8.9%)	T42.6: poisoning: other antiepileptic and sedative–hypnotic drugs	11
			T75.1: drowning and nonfatal submersion	11
			T17.9: foreign body in respiratory tract, part unspecified	6
			T40.2: poisoning: other opioids	6
			T42.4: poisoning: benzodiazepines	6
			T51.9: toxic effect: alcohol unspecified	5
			T90.9: sequelae of unspecified injury of head	5
V	F00–F99: mental and behavioral disorders	76 (5.6%, 4.4%–6.9%)	F10.2: mental and behavioral disorders due to use of alcohol (dependence syndrome)	22
			F81.9: developmental disorder of scholastic skills unspecified	20
			F19.2: mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	11
			F03: unspecified dementia	7
XX	V01–Y98: external causes of morbidity and mortality	74 (5.4%, 4.3%–6.8%)	X42: accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified	9
			W74: unspecified drowning and submersion	6
			W78: inhalation of gastric contents	5
			Y12: poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified, undetermined intent	5
			W65: drowning and submersion while in bathtub	<5
XVII	Q00–Q99: congenital malformations, deformations, and chromosomal abnormalities	72 (5.3%, 4.1%–6.6%)	Q90.9: Down syndrome, unspecified	27
			Q05.9: spina bifida, unspecified	5
XI	K00–K93: diseases of the digestive system	61 (4.5%, 3.4%–5.7%)	K70.9: alcoholic liver disease, unspecified	11
			K74.6: other and unspecified cirrhosis of liver	5
II	C00–D48: neoplasms	47 (3.4%, 2.5%–4.6%)	C71.9: malignant neoplasm: brain, unspecified	9
			C50.9: malignant neoplasm: breast, unspecified	5

(Continues)

TABLE 5 (Continued)

ICD-10 chapters	ICD-10-coded causes of death as chapters	Times a code from this chapter was used as a cause of death, *n* (% of total, 95% CI)	ICD-10-coded causes of death as individual codes within chapters	Times each individual code was used as a cause of death, *n*
IV	E00–E90: endocrine, nutritional, and metabolic diseases	41 (3.0%, 2.2%–4.1%)	E14.9: unspecified diabetes mellitus, without complications	8
			E11.9: type 2 diabetes mellitus	5
XVIII	R00–R99 (excluding R56.8): other symptoms, signs, and abnormal clinical/lab findings not elsewhere classified	38 (2.8%, 2.0%–3.8%)	R68.8: other specified general symptoms and signs	13
			R09.0: asphyxia	6
I	A00–B99: certain infectious and parasitic diseases	28 (2.1%, 1.4%–3.0%)	A41.9: sepsis, unspecified	15
			B18.2: chronic viral hepatitis C	5
XIV	N00–N99: diseases of the genitourinary system	21 (1.5%, 1.0%–2.3%)	N19: unspecified kidney failure	5
III; XVI; VII–VIII; XII; XII	D50–D89: diseases of blood and blood-forming organs and certain disorders involving immune mechanisms; P00–P96: perinatal diseases; H00–H95: diseases of sense organs; L00–L99: diseases of the skin and subcutaneous tissue	7 (.5%, .2%–1.1%)	Each code	<5
XIII	M00–M99: musculoskeletal and connective tissue diseases	6 (.4%, .2%–1.0%)	Each code	<5
XV	O00–O99: pregnancy, childbirth, and puerperium	0 (.0%)	N/A	N/A
Total		1365		

Note: All remaining ICD-10-coded causes of death as individual codes within chapters were used less than five times and are not shown. MCOD analysis takes into account all causes of death listed in the death records of a population for whom at least one of the causes of death was epilepsy (G40–G41, R56.8) in each individual person. In this way, all of the various mechanisms by which epilepsy-related death may have occurred are considered.

Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases 10th Revision; MCOD, multiple cause of death; N/A, not applicable; SUDEP, sudden unexpected death in epilepsy.

suicidality, and psychiatric problems, and it may be that more needs to be done to manage mental health problems in PWE in Scotland. Health care services may also need to be re-evaluated to facilitate acute seizure- and epilepsy-related hospital admissions translating into outpatient neurology care, as we demonstrate a disparity between these areas. The reasons for this remain unclear and require further investigation, particularly as outpatient neurology care is related to improved clinical outcomes for PWE.[38] Furthermore, excess mortality in PWE has been linked to increased social deprivation in England,[39] and we demonstrate similar trends in Scotland, where the majority of epilepsy-related deaths occurred in the two most deprived SIMD quintiles. This finding is also seen in many other conditions in Scotland,[40] and illustrates how widespread the problem of social deprivation is, suggesting that generic strategies for improving social mobility and support could be as effective for epilepsy as for other conditions.

As most young adults with epilepsy want to know about SUDEP,[41] it is likely they would also want to know about other epilepsy-related causes of death. We show that SUDEP constituted 30% of young adult epilepsy-related deaths (increasing to 45% in the "worst-case" scenario analysis). This suggests that, as a whole, the non-SUDEP epilepsy-related causes of death were at least as common (if not more common) than SUDEP. This view is emerging in recent literature,[6] and is supported by systematic review evidence.[5] This is an important area to research further, as it potentially opens up additional targets for epilepsy mortality advice and prevention beyond the SUDEP-specific targets, which tend to predominate research.[6] Mechanisms involved in the non-SUDEP epilepsy-related causes of death we identified included aspiration pneumonia, cardiac arrest, cerebral palsy, AED poisoning, drowning, alcohol dependence, narcotic poisoning, Down syndrome, and brain neoplasms. Some of these causes were not included in a recently proposed classification system for epilepsy-related deaths,[6] and it would seem plausible to consider their addition in future iterations. It will also be important to further corroborate the estimated burden of potentially avoidable epilepsy-related deaths identified using RDAM 2016 with other sources of clinical information including autopsy reports, medical records, general practice (GP) records, and family/physician interview.

Our finding of fewer epilepsy-related deaths in those aged ≥55 years than in the general population should be interpreted with caution, as there is known to be an underestimation of epilepsy-related mortality among older adults.[6] The alleged incidence of SUDEP, for example, declines markedly after age 50 years, comprising 8% of all cases in 51–60-year-olds, 3% among 61–70-year-olds, and 1% in individuals aged >70 years.[6] However, older people are not immune to SUDEP.[6] The lack of reported cases reflects that when elderly PWE die suddenly, autopsies are rarely performed, and when they are, priority tends to be placed on general medical pathologies such as co-existent cardiovascular disease.[6] In the current study, an autopsy was performed in only 6% of those who died aged ≥55 years. Furthermore, in younger people, there is a preponderance of temporal lobe seizures,[42] the semiology of which is well recognized. In older people, most seizures are of extratemporal onset and diverse in semiology, and convulsions are relatively rare.[42] Lack of awareness that an unusual episodic event might be ictal in origin can prevent diagnosis and therefore cause-of-death attribution.[42] Additionally, particularly in high-income countries where many older people live alone, eyewitness accounts are often unavailable, further compounding the potential for ictal underestimation.[42] However, notwithstanding the potential for underreporting of epilepsy-related deaths among older groups, it also remains possible that a heavy burden of premature epilepsy-related mortality in high-risk younger groups acts to leave lower risk groups growing older and thereby lowers the relative burden of epilepsy-related deaths in the older groups. This requires further investigation.

4.3 | Strengths and limitations

This is the first national study of epilepsy-related deaths in Scotland. We include an MCOD data analysis novel to epilepsy mortality literature to identify the various mechanisms of epilepsy-related death in high-risk groups. We also use the ONS's RDAM 2016 on epilepsy mortality data for the first time, signaling what proportion were potentially avoidable. The study is strengthened by case ascertainment from two mandatory national datasets, meaning that virtually the entire Scottish population of interest is studied. These are enriched with information from three additional datasets that add to the depth of information studied. The primary care dataset contained more Scottish GPs than others, including the Health Improvement Network and the Clinical Practice Research Datalink.[26] The study also benefitted from using the optimal case-ascertainment codes previously validated, with positive predictive values of 91%.[26] However, this means that up to 9% of the alleged epilepsy-related deaths we identified may have been in subjects who did not have epilepsy. This is a small number that is within the expected false positive margin of any study using administrative data to capture epilepsy,[25] and it is unlikely to change our overall conclusions, as these were population-based and frequently

underpinned by autopsy. The study is also likely to have benefitted from the cause-of-death quality assurance processes set up to improve Scottish death certification through NRS,[26] the robustness of which was highlighted recently.[21]

The study limitations included inability to assess a live population at risk dataset, meaning we were unable to calculate MR using person-years at risk as a denominator. We were also limited by lack of access to a national control group dataset without epilepsy to compare our estimates against, including the MCOD data. Finally, we were unable to control for other mortality risk factors such as smoking and obesity because of lack of an appropriate national dataset containing these.[8] Our findings should therefore help stimulate the development of appropriate national datasets to assess these areas. In particular, future studies could use case–control data to assess combinations of causes of death in cases with epilepsy compared with those combinations of death in controls without epilepsy to assess for the relationship. We know that in decreasing order, the 10 most frequently occurring principle causes of premature death in the general Scottish population <75 years old are lung cancer, myocardial infarction, drug poisoning, ischemic heart disease, breast cancer, chronic obstructive pulmonary disease (COPD), atherosclerotic heard disease, infected COPD, esophageal cancer, and hanging.[43] Our MCOD data signpost a different set of top 10 causes to this when epilepsy is involved (Table 5), highlighting rationale for a future case–control MCOD study. Our study provides a robust methodological framework for the data linkage and MCOD case-ascertainment methods future researchers could use to undertake such a study in Scotland.

5 | Conclusions

This study gives an indication that epilepsy-related deaths are potentially a major public health problem in Scotland and highlights several areas in which further work is likely to help further refine the exact scale of the problem. The study illustrates the validity of using linked administrative data to identify potential trends in disease. Further work will be required to establish whether Scotland is representative of other developed countries in its distribution of different epilepsy-related causes of death, although we have little reason to suspect that this would not be the case, based on ongoing follow-up work from a recent systematic review of epilepsy-related deaths.[5]

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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