Journal of Neurology (2023) 270:3527–3536
https://doi.org/10.1007/s00415-023-11701-6

ORIGINAL COMMUNICATION

# Mortality risk in adults with intellectual disabilities and epilepsy: an England and Wales case–control study

James J. Sun[1] · Lance Watkins[2,3] · William Henley[4] · Richard Laugharne[5,6] · Heather Angus-Leppan[1] · Indermeet Sawhney[7] · Meissam Moghaddassian Shahidi[7] · Kiran Purandare[8] · Mogbeyiteren Eyeoyibo[9] · Mark Scheepers[10] · Geraldine Lines[10] · Robert Winterhalder[11] · Bhathika Perera[12] · Benjamin Hyams[5] · Samantha Ashby[13] · Rohit Shankar[5,6,14]

Received: 15 March 2023 / Revised: 29 March 2023 / Accepted: 30 March 2023 / Published online: 6 April 2023


## Abstract

**Background** People with epilepsy (PWE) and people with intellectual disabilities (ID) both live shorter lives than the general population and both conditions increase the risk of death further. We aimed to measure associations between certain risk factors for death in PWE and ID.

**Methods** A retrospective case–control study was conducted in ten regions in England and Wales. Data were collected on PWE registered with secondary care ID and neurology services between 2017 and 2021. Prevalence rates of neurodevelopmental, psychiatric and medical diagnoses, seizure frequency, psychotropic and antiseizure medications (ASM) prescribed, and health activity (epilepsy reviews/risk assessments/care plans/compliance etc.) recorded were compared between the two groups.

**Results** 190 PWE and ID who died were compared with 910 living controls. People who died were less likely to have had an epilepsy risk assessment but had a greater prevalence of genetic conditions, older age, poor physical health, generalized tonic–clonic seizures, polypharmacy (not ASMs) and antipsychotic use. The multivariable logistic regression for risk of epilepsy-related death identified that age over 50, medical condition prevalence, antipsychotic medication use and the lack of an epilepsy review in the last 12 months as associated with increased risk of death. Reviews by psychiatrists in ID services was associated with a 72% reduction in the odds of death compared neurology services.

**Conclusions** Polypharmacy and use of antipsychotics may be associated with death but not ASMs. Greater and closer monitoring by creating capable health communities may reduce the risk of death. ID services maybe more likely to provide this holistic approach.

James J. Sun, Lance Watkins have contributed equally to this work.

✉ Rohit Shankar
rohit.shankar@plymouth.ac.ukAuthors and Affiliations

1 Royal Free London NHS Foundation Trust, London, UK
2 Swansea Bay University Health Board, Port Talbot, UK
3 University of South Wales, Pontypridd, UK
4 University of Exeter Medical School, Exeter, UK
5 Cornwall Partnership NHS Foundation Trust, Truro, UK
6 University of Plymouth Peninsula School of Medicine, Truro, UK
7 Hertfordshire Partnership University NHS Foundation Trust, St Albans, UK
8 Central and North West London NHS Foundation Trust, London, UK
9 Kent and Medway NHS and Social Care Partnership Trust, Gillingham, UK
10 Gloucestershire Health and Care NHS Foundation Trust, Gloucestershire Health and Care NHS Foundation Trust, Brockworth, UK
11 Oxleas NHS Foundation Trust, Bromley on Bow, UK
12 Barnet, Enfield and Haringey Mental Health NHS Trust, London, UK
13 SUDEP Action, Wantage, UK
14 Chy Govenek, Threemilestone Industrial Estate, Highertown, Truro TR4 9LD, Cornwall, UK

**Keywords** Developmental disabilites · Premature mortality · Seizures · Multi-morbidity · Antipsychotics prescribing · Neurodevelopment

## Introduction

### Epilepsy and premature mortality

The life expectancy for people with active epilepsy is at least 10 years lower than the general population [1, 2]. Furthermore, the proportion of preventable deaths in people with epilepsy (PWE) are higher than other chronic life-threatening conditions [3]. A national audit in the United Kingdom (UK) found that 42% of epilepsy related deaths were potentially avoidable [4]. A systematic review by the Mortality Task Force of the International League Against Epilepsy (ILAE) found no evidence that this is improving [5, 6].

A systematic review of epilepsy-related mortality demonstrates that all cause-mortality remains elevated with no improvement for decades (median standardised mortality ratio (SMR) 2.3–3.4) [6]. This contrasts with reductions in other causes of mortality, as illustrated by a 16.4% reduction in all-cause mortality in a large population-based study in the United States (USA) [7]. A retrospective cohort analysis with controls investigating epilepsy and mortality in the USA between 2005 and 2014, found that deaths increase by 69% over 10 years up to 2014 [8]. Whilst in the UK, 45% of the deaths of PWE under the age of 35 were directly related to their epilepsy [9]. These findings are consistent with a Public Heath England Report (2001–14) showing a 70 percent increase in epilepsy related deaths [3].

### Epilepsy and intellectual disabilities

Just over 2% of the population of England and Wales are recognised to have intellectual disabilities (ID). Nearly a quarter (22.5%) have epilepsy [10]. PWE and ID are recognised to have high levels of multimorbidity, polypharmacy and epilepsy related risks [11].

Awareness has grown in the last 20 years of the elevated mortality for all PWE, and those with ID in particular. In studies comparing mortality in people with ID and epilepsy compared to ID without epilepsy, the risk of death has been found to be two or more times greater [10]. Epilepsy is the most prevalent long term health condition associated with ID and has been associated with one-third of the deaths of people with ID [12].

PWE and ID, particularly children and young adults are at higher risk of dying than those with epilepsy alone [13]. All-cause SMR for PWE and ID are three to four times higher than the general population [14–16]. Mortality rates are higher for younger people (7 times) and for people with more severe ID (13 times) [16, 17]. More than half of the potentially preventable deaths identified in people with ID were epilepsy related [17].

This case–control study examines factors relating to mortality in PWE with ID. The aim of this investigation is to identify risk factors for all-cause mortality amongst adults with epilepsy and ID. This may help direct future interventions to reduce risk.

## Methods

### Study design

We conducted an England and Wales wide multi-centre retrospective case–control study using routine clinical information from controls and recorded deaths of PWE and ID from the same centres. Mortality risk factors were characterised to look for associations between individual factors or combinations of factors and mortality. Three related lines of inquiry were conducted. Firstly, all PWE and ID irrespective of their cause of death were compared with controls. Then, those PWE and ID who died of epilepsy as a primary cause were compared to the controls. Finally, a comparison made to see if outcomes for those with mild ID differ from those with moderate to profound ID.

The STROBE checklist was followed for this case–control study (Supplementary file 1). Data interpretation was undertaken with SUDEP Action, a national UK charity which specializes in raising awareness of Sudden Unexpected Death in Epilepsy (SUDEP) and other forms of epilepsy related mortality.

### Controls

Data from the Epilepsy in Intellectual Disability (Epi-IDNA) study was used to form the control group. Epi-IDNA was a cross-sectional national study investigating epilepsy related multimorbidity, polypharmacy and seizure risk in adults with intellectual disability [18]. The Epi-IDNA protocol was a consensus questionnaire developed by specialists in epilepsy and intellectual disabilities in consultation with experts by experience. Participating centres for the study had identified eligible cases through automated and manual searches of electronic health records between October 2019 and June 2020 [18].

### Cases and data collection

Each NHS centre identified cases (people with ID who had died) in the 5-year period 2017–2021. The national program LeDeR commenced in 2017 which identified all deaths of people with ID [4]. The last report was of 2021 [12]. Each centre had access to their respective submissions to the LeDeR program. Inclusion criteria were death during the specified period, aged > 18 years old, presence of intellectual disability and a diagnosis of epilepsy. All cases were known to the intellectual disability or neurology service at the time of death. Cases were identified through automated and manual searches of electronic health records as well as through interrogation of local registries.

The electronic patient record for each identified case was examined. Adults with attention deficient hyperactivity disorder (ADHD) or autism spectrum disorder, without a co-morbid intellectual disability, were excluded. Severity of intellectual disabilities was divided as per the ICD criteria into two groups i.e. mild and moderate/profound ID.

Data on demographics, health background, epilepsy profile, medications and epilepsy mortality/SUDEP risk factors were collected as with our previous study using the validated SUDEP and Seizure Safety checklist [18, 19]. Data from each centre were entered into a secure electronic database: Research Electronic Data Capture (REDCap) to allow pooled analysis [20].

### Statistical analysis

Demographic and clinical characteristics for the cases and controls were summarised by the mean and standard deviation (SD) for continuous data, and the number and percentage for categorical data. Univariable associations between potential risk factors and mortality status (case/control) were assessed using Fisher's exact test. Where risk factors in the SUDEP and Seizure Safety checklist were explicitly recorded as "unknown", these values were coded as an independent category to assess the potential predictive power of this information on a patient not being captured. Other sources of missing data were handled using a complete cases approach. Multivariable logistic regression was performed to estimate odds ratios (ORs) for risk prediction modelling. Variables were selected for inclusion based on a manual stepwise procedure. As an a priori threshold, any variables with ≥ 30% of their values missing in cases or controls were excluded from the multivariable analysis. Discrimination performance of the risk prediction models was assessed by the area under the receiver operating characteristic (ROC) curve. The functional form of the relationship between log-odds of mortality risk and numerical variables, such as age and number of medications, was assessed using logistic generalised additive models (GAMs) with cubic splines. The multivariable logistic regression analysis was repeated separately in the sub-populations with mild ID and moderate-to-profound ID to assess potential heterogeneity in risk profile by ID severity. All analyses were performed using the R environment for statistical computing.

### Ethics and standard protocol approval

Each participating NHS centre included in the study registered the project as a local audit or service evaluation and conducted a Data Protection Impact Assessment (DPIA) and gaining approval from their local information governance (IG) leads. Only de-identified data were submitted to the central REDCap database. This process was overseen by an IG lead. REDCap was used to collect data in compliance with the General Data Protection Regulation (GDPR). This study did not require formal ethical approval as per the NHS Health Research Authority tool (http://www.hra-decisiontools.org.uk/research/index.html supplementary information 2).

### Data sharing

Anonymised participant data and the data dictionary are available along with the study protocol and can be requested from the corresponding author.

## Results

This study included 190 deceased cases (101 male, 89 female) and 910 living controls (546 male, 365 female, 1 other) (of which 904 had information on severity of ID) collected from 10 different NHS Trusts offering specialised care for people with epilepsy and intellectual disabilities in England and Wales. Mean age at death for the cases was 53 ± 17 years (range 18–86) and mean age at assessment for the controls was 40 ± 15 years (range 18–92).

Demographic, general clinical and epilepsy-specific characteristics are summarised in Table 1. In univariable analysis, cases were more likely to be aged over 40 ($p < 0.001$), have one or more physical health comorbidities ($p < 0.001$), have a genetic condition ($p = 0.03$), to be taking a total more than five medications ($p < 0.001$) or to be on an anti-psychotic medication. Cases were less likely than controls to have a psychiatric diagnosis ($p = 0.01$), a diagnosis of ASD ($p < 0.001$) or ADHD ($p = 0.01$), have generalised tonic–clonic seizures ($p < 0.001$), be on two or more ASMs ($p = 0.04$) or to have had an epilepsy review in the last 12 months ($p < 0.001$). Routine collection of clinical data was more incomplete for cases than control: cases were more likely to have an unknown seizure frequency ($p < 0.001$) and epilepsy duration ($p < 0.001$), unknown alcohol and drug status ($p < 0.001$), unknown record of Emergency Department (ED) attendance ($p < 0.001$) and discussion of SUDEP and seizure safety risks ($p < 0.001$).

**Table 1** Selected characteristics of cases and controls in the Epi-IDNA mortality study

| | Ncontrol | Ncase | %control | %case | *p*-value |
|---|---|---|---|---|---|
| Severity of ID | | | | | |
| Mild ID | 320 | 48 | 35% | 29% | 0.09 |
| Moderate-profound ID | 584 | 120 | 65% | 71% | |
| Gender | | | | | |
| Male | 546 | 101 | 60% | 53% | 0.25 |
| Female | 365 | 89 | 40% | 47% | |
| Age | | | | | |
| Age > 40 | 395 | 142 | 43% | 75% | < 0.001 |
| Age < 40 | 517 | 48 | 57% | 25% | |
| Genetic condition | | | | | |
| Yes | 194 | 48 | 21% | 29% | 0.03 |
| No | 710 | 116 | 79% | 71% | |
| Physical health | | | | | |
| Yes | 531 | 149 | 59% | 85% | < 0.001 |
| No | 373 | 26 | 41% | 15% | |
| Psychiatric diagnosis | | | | | |
| Yes | 305 | 41 | 34% | 24% | 0.01 |
| No | 599 | 133 | 66% | 76% | |
| ASD | | | | | |
| Yes | 337 | 29 | 37% | 17% | < 0.001 |
| No | 567 | 146 | 63% | 83% | |
| ADHD | | | | | |
| Yes | 59 | 3 | 7% | 2% | 0.01 |
| No | 845 | 170 | 93% | 98% | |
| Bilateral tonic–clonic motor seizures | | | | | |
| Yes | 565 | 90 | 63% | 51% | < 0.001 |
| No | 328 | 86 | 37% | 49% | |
| Seizure frequency | | | | | |
| Unknown | 93 | 82 | 10% | 47% | < 0.001 |
| Known | 799 | 91 | 90% | 53% | |
| > 5 medications | | | | | |
| Yes | 339 | 115 | 39% | 65% | < 0.001 |
| No | 532 | 62 | 61% | 35% | |
| 2 + ASM meds | | | | | |
| Yes | 584 | 101 | 69% | 61% | 0.04 |
| No | 257 | 65 | 31% | 39% | |
| Anti-psychotic medications | | | | | |
| Yes | 236 | 66 | 27% | 39% | < 0.001 |
| No | 650 | 105 | 73% | 61% | |
| Epilepsy review | | | | | |
| Yes | 812 | 119 | 92% | 75% | < 0.001 |
| No | 66 | 40 | 8% | 25% | |
| Epilepsy duration | | | | | |
| Unknown | 92 | 76 | 10% | 45% | < 0.001 |
| Known | 786 | 94 | 90% | 55% | |
| A&E attendance | | | | | |
| Unknown | 37 | 55 | 4% | 31% | < 0.001 |
| Known | 841 | 125 | 96% | 69% | |
| Compliance issues | | | | | |
| Yes | 71 | 15 | 8% | 10% | 0.42 |
| No | 807 | 134 | 92% | 90% | |

**Table 1** (continued)

| | Ncontrol | Ncase | %control | %case | *p*-value |
|---|---|---|---|---|---|
| Alcohol | | | | | |
| Unknown | 5 | 33 | 1% | 18% | < 0.001 |
| Known | 872 | 146 | 99% | 82% | |
| Drugs | | | | | |
| Unknown | 4 | 34 | 0% | 19% | < 0.001 |
| Known | 874 | 146 | 100% | 81% | |
| Care plan | | | | | |
| Yes | 640 | 83 | 73% | 66% | 0.14 |
| No | 238 | 42 | 27% | 34% | |
| SUDEP and Seizure Safety discussion | | | | | |
| Unknown | 0 | 76 | 0% | 42% | < 0.001 |
| Known | 878 | 104 | 100% | 58% | |

*ASD* Autism Spectrum Disorder, *ADHD* Attention deficit Hyperactivity Disorder

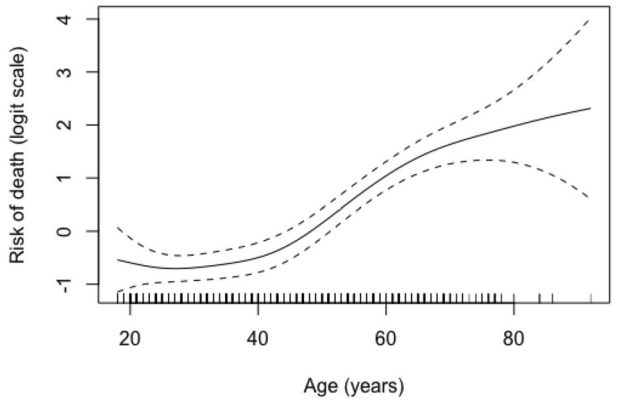


**Fig. 1** Functional form of the relationship between risk of death and age for patients in the Epi-IDNA mortality study

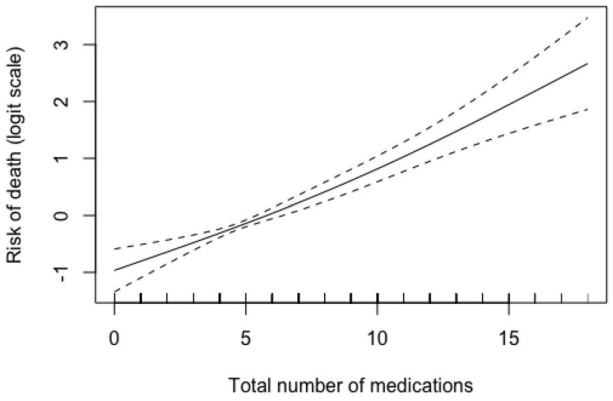


**Fig. 2** Functional form of the relationship between risk of death and total number of medications for patients in the Epi-IDNA mortality study

There was a non-linear relationship between the log-odds of death and age, with the risk of death flat before age 40 and then increasing sharply (Fig. 1; expected degrees of freedom from logistic GAM = 3.67, $p < 0.001$). The relationship between risk of death and total number of medications was close to linear on the logit scale (Fig. 2; expected degrees of freedom from logistic GAM = 1.45, $p < 0.001$). There was no association between mortality risk and number of ASMs (Fig. 3; expected degrees of freedom from logistic GAM = 1.40, $p = 0.31$).

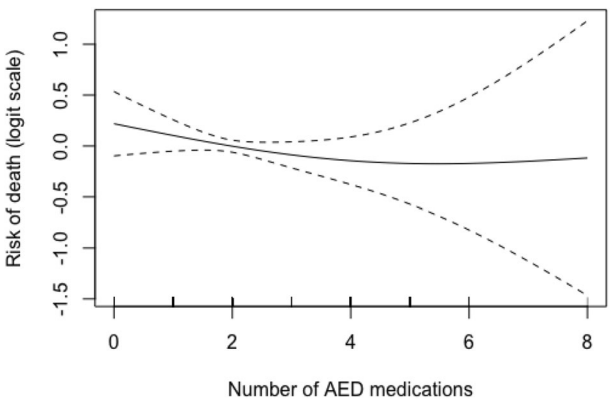


**Fig. 3** Functional form of the relationship between risk of death and number of ASMs for patients in the Epi-IDNA mortality study

## Multivariable analysis

### All-cause mortality

Table 2 shows the selected multivariable logistic regression model for risk of death. After adjustment for age, comorbidities and use of medications, odds of death were reduced by 84% for PWE and ID that had had a review of their epilepsy in the last 12 months. The area under the receiver operating characteristic (ROC) curve for the

**Table 2** Multivariable logistic regression model for risk of all-cause mortality in Epi-IDNA case–control study

| | OR | 95% CI | *p*-value |
|---|---|---|---|
| Age | | | |
| < 40 | 1.00 | | |
| 40–50 | 0.92 | 0.43–1.96 | 0.82 |
| 50–60 | 3.87 | 2.31–6.50 | < 0.001 |
| > 60 | 4.63 | 2.73–7.85 | < 0.001 |
| Physical health | | | |
| Yes | 4.11 | 2.33–7.24 | < 0.001 |
| No | 1.00 | | |
| Psychiatric diagnosis | | | |
| Yes | 0.26 | 0.15–0.45 | < 0.001 |
| No | 1.00 | | |
| ASD | | | |
| Yes | 0.45 | 0.26–0.78 | 0.004 |
| No | 1.00 | | |
| Number of medications (per drug) | 1.16 | 1.09–1.23 | < 0.001 |
| Anti-psychotic medications | | | |
| Yes | 2.99 | 1.75–5.11 | < 0.001 |
| No | 1.00 | | |
| Epilepsy review | | | |
| Yes | 0.16 | 0.09–0.29 | < 0.001 |
| No | 1.00 | | |

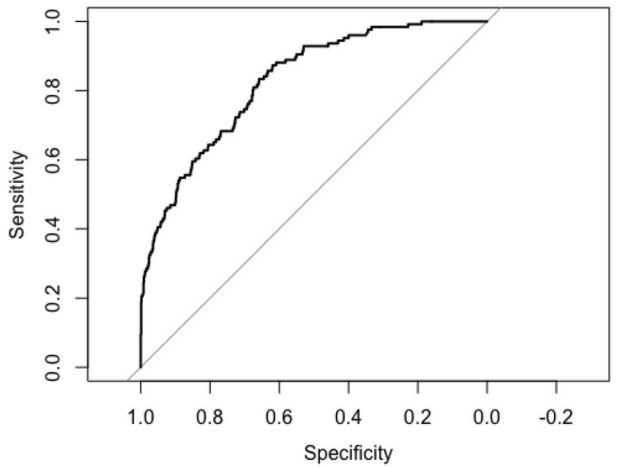


**Fig. 4** ROC curve for logistic regression model for mortality risk (AUC = 0.84)

multivariable model was 0.84 (Fig. 4). Mortality risk prediction models including the same set of risk factors gave similar risk estimates and model discrimination when fitted separately in the sub-populations of people with mild ID and moderate-to-profound ID (Supplementary information 3; AUC 0.83 and 0.84 respectively).

**Table 3** Effect of type of service reviewing patient's epilepsy in multivariable logistic regression model for risk of death

| Type of service | OR | 95% CI | *p*-value |
|---|---|---|---|
| No review in last 12 months | 3.95 | 1.96–8.08 | < 0.001 |
| Neurologist | 1.00 | | |
| GP | 0.46 | 0.12–1.36 | 0.19 |
| Psychiatrist | 0.38 | 0.22–0.68 | 0.001 |
| Specialist Epilepsy Nurse | 1.82 | 0.87–3.82 | 0.11 |

**Table 4** Multivariable logistic regression model for risk of death from epilepsy in Epi-IDNA case–control study

| | OR | 95% CI | *p*-value |
|---|---|---|---|
| Age | | | |
| < 50 | 1.00 | | |
| 50 + | 2.44 | 1.06–5.59 | 0.03 |
| Physical health | | | |
| Yes | 2.71 | 1.10–7.74 | 0.04 |
| No | 1.00 | | |
| Psychiatric diagnosis | | | |
| Yes | 0.16 | 0.04–0.48 | 0.004 |
| No | 1.00 | | |
| Duration of epilepsy | | | |
| < 5 years | 1.00 | | |
| 5–15 years | 0.35 | 0.04–1.89 | 0.24 |
| > 15 years | 0.16 | 0.05–0.58 | 0.002 |
| Unknown | 0.38 | 0.09–1.66 | 0.19 |
| Seizure frequency | | | |
| > Weekly | 1.00 | | |
| > Monthly | 0.53 | 0.18–1.52 | 0.24 |
| > 3 monthly | 0.28 | 0.04–1.18 | 0.12 |
| > Annually | 0.18 | 0.03–0.74 | 0.03 |
| < Annually | 0.07 | 0.003–0.38 | 0.12 |
| Unknown | 1.33 | 0.38–4.66 | 0.66 |

The multivariable model was extended to allow for comparison of mortality risk estimates by the type of service providing care to the patient (Table 3). The lack of an epilepsy review in the last 12 months was associated with a nearly fourfold increase in risk of death compared to review by a neurology service. Review by an intellectual disability service was associated with a 72% reduction in the odds of death compared to review by a neurology service.

### Epilepsy-specific mortality

Table 4 shows the multivariable logistic regression model for risk of epilepsy-related death. Age over 50 and prevalence of a physical condition were associated with increased risk of death, as in the model for all-cause mortality. Psychiatric

diagnosis was associated with a lower risk of death. None of the identified death were recorded as suicide. Epilepsy-specific risk factors associated with increased mortality were increased seizure frequency and more recent epilepsy diagnosis. Of the 48 who had a genetic condition Down syndrome ($n=31$) was the most represented. Others included Angelman syndrome ($n=1$), Fragile X syndrome ($n=1$) and others ($n=12$). No genetic mutations associated with channelopathies were identified.

#### Sudden Unexpected Death in Epilepsy (SUDEP)

This investigation identified five deaths attributed directly to SUDEP. None of these patients were on anti-psychotic or other psychotropic medication. This small cohort were on a median of five total medications and two ASMs.

## Discussion

This case–control study of deaths in PWE and ID suggests an association between deaths and fewer epilepsy reviews and fewer recordings in health notes of the duration of epilepsy, seizure frequency, alcohol use, drug use, attendance at ED, and discussion of SUDEP and seizure related risks. All of these form part of vigilant monitoring of care by capable health communities. This study provides evidence that closer monitoring of PWE with ID may reduce deaths.

In addition, there are associations with deaths for people with older age, poor health and those with genetic conditions. These associations are not surprising as they are associated with deaths in the general population. What is surprising was the lack of an association between the severity of the ID and death as life expectancy diminishes with severity of ID [12].

There are associations with medication use. However, a higher number of ASMs was associated with fewer deaths. PWE and ID are more likely to have pharmacoresistant epilepsy and so there might be a good reason for the increased numbers of ASMs. This may be reassuring that these medications are being used safely and appropriately, and use of multiple ASMs may protect these patients from death. It is surprising that those who died had lower prevalence of tonic–clonic seizures. Possibly patients with more severe epilepsy are more actively treated with multiple ASMs and greater control is achieved. It is also likely that more subtle seizures are sometimes overlooked and undertreated.

Polypharmacy ($>5$), aside from ASMs, and the use of antipsychotics are associated with deaths. The percentage of patients with an ID in England being prescribed antipsychotics was approximately 15% between 2016–2017 and 2020–2021 [21]. While those without an ID being prescribed antipsychotics was 0.9% [21]. In our study, while 27% of controls were on antipsychotics, so were 39% of the deaths. This significantly high levels of antipsychotic prescribing, possibly long term and its relation to premature mortality is a major concern. Since 2015 there is a national program called STOMP focused on reducing the overprescribing of psychotropics particularly anti-psychotics in England [22]. However, while there have been modest successes since its launch in 2016 to 2021 of reducing antipsychotics from 15.7 to 14.8%, it has struggled to encompass the complexities of prescribing especially to vulnerable sub-populations such PWE and ID [21, 23, 24]. Our study, though in specialist care brings specific focus on PWE and ID given the high rates of antipsychotic prescribing and associated mortality. While the high rates of antipsychotic prescribing is associated with global epilepsy related deaths a specific look at the five SUDEPs showed none were on any antipsychotics or psychotropics. Given the association of SUDEP to cardiac QTc prolongation this is an interesting finding. However, it might have been associated with other epilepsy deaths which might have been SUDEPs but not diagnosed as such. This highlights the importance of a comprehensive post-mortem work up and diagnosis for suitable learning.

The rates of autism, ADHD and a psychiatric diagnosis were lower in those who died compared with controls, which offers some reassurance for those with these additional concerns. Patients who died were more likely to be treated by neurology services than ID services. It could be argued that neurology services maybe associated with looking after PWE and ID who have a higher rate of co-morbidities. The neurology services across England and Wales are generally focused on epilepsy management and not on holistic care which appears a more pressing need for PWE and ID [25]. It is also likely that there is a challenge to provide reasonable adjustments to more complex patients with ID [26]. When under ID services patients are more likely to have 'wrap-around' care from a multi-disciplinary team including psychology, speech and language therapists, nursing, occupational therapists, dietitians etc. and this may be protective. Further, in the last decade ID services in England have become more aware of the concerns people with ID face particularly regards physical health concerns (including epilepsy) and premature mortality due to a range of national reports and high-quality publications [12, 26–28]. It could be that this difference between ID services and neurology services is a positive dividend of that.

The risk of epilepsy-related deaths specifically; age over 50, physical co-morbidity, seizure frequency, and recency of epilepsy diagnosis were all associated with increased risk of death.

## Mortality risk factors in PWE and ID

Although data exist on risk factors for SUDEP and seizure safety in PWE and ID, there is a limited understanding of factors contributing to general mortality in this population [19]. In PWE and ID, it is difficult to untangle how much of the increased mortality relates to underlying conditions rather than the epilepsy per se, because higher mortality in ID correlates with the severity of disability, and the severity of epilepsy. Examining the broader topic of epilepsy related deaths (ERD), rather than sudden unexpected death in epilepsy (SUDEP) alone (which accounts for about 50% of deaths in the general epilepsy population) maximises the chances of successful interventions [29].

Studies comparing cohorts of PWE found that there is an increased mortality risk for those with ID [30, 31]. However, the risk was not significant in multivariable analysis, with abnormal neurological examination being the only significant determinant [31]. Other studies have found that severe cognitive impairment was associated with an increased risk in those with epilepsy, but only in those who were not in seizure remission [32]. This highlights the need to analyse risk factors individually and in combination, to understand the most important interventions to reduce deaths.

In the Leicester Intellectual Disability Register, from 1993 to 2010 SUDEP was the second most common cause of death amongst adults with epilepsy and intellectual disability [33]. In this study, there were five SUDEPs. It is possible that some other epilepsy deaths did not get a suitable workup such as a neuropathological autopsy to diagnose or rule out SUDEP. It is important there be clinical confidence in post-mortem feedback.

Risk appears to be associated with seizure type and frequency in PWE and ID, with those who have not had a seizure in the last year having no increase in mortality risk within this population [34–36]. Some of these deaths could be potentially preventable with medical review [37]. There is clear evidence that people with ID suffer delayed medical diagnosis of treatable co-morbidities, and regular health checks can reduce morbidity and mortality [38]. A finding of the low rates of genetic syndromes (other than for Down syndrome), in particular a lack of any channelopathies, suggests that more work clinically could be done to explore for genetic conditions in this population given the emergence of newer treatments.

Frequent major seizures often reflect the severity of the neurological diagnosis, but may be modifiable, depending on the neurological condition. Even in treatment resistant epilepsy, improved monitoring and safety provision potentially reduces risk [39]. Many studies echo the finding that epilepsy related deaths occur in people who have not had a medical review in the previous 12 months [4]. An increase in seizure frequency in the preceding 6 months is a strong risk factor for sudden unexpected death in epilepsy (SUDEP) in PWE [35].

## Limitations

These data were obtained from the caseloads of secondary care ID services or neurology services. This population are likely to be more severe in the degree of ID and have higher rates of comorbid conditions. The samples were gained by reviews of NHS records and were not a general population sample.

As a case–control study, we can only report associations and make no conclusion on causations. There may be confounding factors that we have not considered. There was no available data about patients receiving psychological support and social assistance which could in theory play a role in reducing deaths.

The mortality data collected for this review was collected in part during the COVID-19 pandemic. Therefore, this may have influenced the number of deaths, and the causes of deaths. We did not compare the quality of electronic health records pre- or post-pandemic. We acknowledge that a limitation of this retrospective observational study is the possibility of incomplete or missing data.

## Implications for clinical care

The results suggest poorer recording of health status and lower frequency of epilepsy review may be associated with deaths. On one level this suggests the positive possibility that close health monitoring of these vulnerable people can reduce the likelihood of death and that the clinical care is effective, a positive message. These data may support the justification of close monitoring of epilepsy care in secondary services. The clinician who should perform these reviews may be either a psychiatrist specialising in ID or a neurologist [40]. Here there was a risk reduction in death when the Person with ID was reviewed by either a psychiatrist specialising in ID or neurologist in the last 12 months but more protection possibly due to the availability of a muti-disciplinary team when the review was via a specialist psychiatrist working with people with ID.

We might hypothesise that the use of antipsychotics and general polypharmacy may be associated with deaths. This would support the minimal use of antipsychotics and keeping doses at the minimum effective dose as well as reducing general polypharmacy as much as possible. However, deaths may be associated with general polypharmacy because people who are ill are put on more medications.

However, it is reassuring that the use of multiple ASMs, normally used in treatment resistant epilepsy, is not

associated with deaths. It may be that using multiple ASMs protect patients from death in this population.

## Implications for research

As these results are associations, further research is needed on the effectiveness of epilepsy review and health monitoring, polypharmacy and the effect of antipsychotics on the mortality of people with ID and epilepsy using prospective methodologies and clinical trials.

## Implications for policy

We must be tentative in suggesting any change in policy as this retrospective case–control study can only report associations and not causations. These data may support the advocacy of regular epilepsy reviews (including assessment of modifiable mortality risks) and health monitoring, close review of general polypharmacy and minimising the use of antipsychotics in people with ID and epilepsy.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11701-6.

**Acknowledgements** Ms Gina Matthews Cornwall Partnership NHS Foundation Trust for information governance support and Ms Sarah Saunders NHS Kernow Clinical Commissioning Group, United Kingdom.

**Funding** No funding was received for this project.

**Data availability** The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Conflict of interest** RS and SUDEP Action are co-developers of the not for profit, non-commercial SUDEP and Seizure Safety Checklist which has been used in the study described here. SA works for SUDEP Action. SA and RS have been involved in the development and promotion of the SUDEP and Seizure safety Checklist. RS has received institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Averelle and GW pharma outside the submitted work. No other author has any disclosures or conflicts to declare.

## References

1. Gaitatzis A, Sander JW (2004) The mortality of epilepsy revisited. Epileptic Disord 6(1):3–13
2. Puteikis K, Mameniškienė R (2021) Mortality among people with epilepsy: a retrospective nationwide analysis from 2016 to 2019. Int J Environ Res Public Health. https://doi.org/10.3390/ijerph181910512
3. Neurology N, Network (2018) INNEoLCI. Deaths associated with neurological conditions in England 2001 to 2014. Data Analysis Report. . Public Health England
4. University, Bristol. O (2019) The Learning Disabilities Mortality Review (LeDeR) Programme, Annual Report, 2019
5. Thurman DJ, Logroscino G, Beghi E et al (2017) The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 58(1):17–26. https://doi.org/10.1111/epi.13604
6. Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM (2019) Epilepsy-related and other causes of mortality in people with epilepsy: a systematic review of systematic reviews. Epilepsy Res 157:106192. https://doi.org/10.1016/j.eplepsyres.2019.106192
7. DeGiorgio CM, Curtis A, Carapetian A, Hovsepian D, Krishnadasan A, Markovic D (2020) Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. BMJ Open 10(8):e035767. https://doi.org/10.1136/bmjopen-2019-035767
8. Greenlund SF, Croft JB, Kobau R (2017) Epilepsy by the Numbers: Epilepsy deaths by age, race/ethnicity, and gender in the United States significantly increased from 2005 to 2014. Epilepsy Behav 69:28–30. https://doi.org/10.1016/j.yebeh.2017.01.016
9. Wojewodka G, Gulliford MC, Ashworth M, Richardson MP, Ridsdale L (2021) 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. BMJ Open 11(10):e052841. https://doi.org/10.1136/bmjopen-2021-052841
10. Robertson J, Hatton C, Emerson E, Baines S (2015) Mortality in people with intellectual disabilities and epilepsy: a systematic review. Seizure 29:123–133. https://doi.org/10.1016/j.seizure.2015.04.004
11. Sun JJ, Perera B, Henley W et al (2022) Epilepsy related multimorbidity, polypharmacy and risks in adults with intellectual disabilities: a national study. J Neurol 269(5):2750–2760. https://doi.org/10.1007/s00415-021-10938-3
12. White A, Sheehan R, Ding J, et al (2021) Learning from lives and deaths - people with a learning disability and autistic people (LeDeR) report for 2021 (LeDeR 2021). Autism and learning disability partnership, King's College, London
13. Liao P, Vajdic CM, Reppermund S, Cvejic RC, Srasuebkul P, Trollor JN (2022) Mortality rate, risk factors, and causes of death in people with epilepsy and intellectual disability. Seizure 101:75–82. https://doi.org/10.1016/j.seizure.2022.07.012
14. Tyrer F, Smith LK, McGrother CW (2007) Mortality in adults with moderate to profound intellectual disability: a population-based study. J Intellect Disabil Res 51(Pt 7):520–527. https://doi.org/10.1111/j.1365-2788.2006.00918.x
15. Hosking FJ, Carey IM, Shah SM et al (2016) Mortality among adults with intellectual disability in England: comparisons with the general population. Am J Public Health 106(8):1483–1490. https://doi.org/10.2105/ajph.2016.303240
16. McCarron M, Carroll R, Kelly C, McCallion P (2015) Mortality rates in the General Irish population compared to those with an intellectual disability from 2003 to 2012. J Appl Res Intellect Disabil 28(5):406–413. https://doi.org/10.1111/jar.12194
17. Hirvikoski T, Boman M, Tideman M, Lichtenstein P, Butwicka A (2021) Association of intellectual disability with all-cause and cause-specific mortality in Sweden. JAMA Netw Open 4(6):e2113014. https://doi.org/10.1001/jamanetworkopen.2021.13014
18. Sun JJ, Perera B, Henley W et al (2022) Correction to: epilepsy related multimorbidity, polypharmacy and risks in adults with intellectual disabilities: a national study. J Neurol 5:2761
19. Shankar R, Cox D, Jalihal V, Brown S, Hanna J, McLean B (2013) Sudden unexpected death in epilepsy (SUDEP): development of a safety checklist. Seizure 22(10):812–817. https://doi.org/10.1016/j.seizure.2013.07.014

20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42(2):377–381. https://doi.org/10.1016/j.jbi.2008.08.010
21. https://digital.nhs.uk/data-and-information/publications/statistical/health-and-care-of-people-with-learning-disabilities/experimental-statistics-2020-to-2021/prescribing. Accessed 7 Mar 2023.
22. https://www.england.nhs.uk/learning-disabilities/improving-health/stomp/. Accessed 7 Mar 2023.
23. Branford D, Sun JJ, Shankar R (2023) Antiseizure medications prescribing for behavioural and psychiatric concerns in adults with an intellectual disability living in England [published online ahead of print, 2023 Feb 14]. Br J Psychiatry 1:23. https://doi.org/10.1192/bjp.2022.182
24. Branford D, Shankar R (2022) Antidepressant prescribing for adult people with an intellectual disability living in England. Br J Psychiatry 221(2):488–493. https://doi.org/10.1192/bjp.2022.34
25. Watkins LV, Linehan C, Brandt C, Snoeijen-Schouwenaars F, McGowan P, Shankar R (2022) Epilepsy in adults with neurodevelopmental disability—what every neurologist should know. Epileptic Disord 24:9–25. https://doi.org/10.1684/epd.2021.1366
26. Watkins L, O'Dwyer M, Kerr M, Scheepers M, Courtenay K, Shankar R (2020) Quality improvement in the management of people with epilepsy and intellectual disability: the development of clinical guidance. Expert Opin Pharmacother 21(2):173–181. https://doi.org/10.1080/14656566.2019.1695780
27. Kennedy N, Brophy S, Kennedy J, Kerr M (2019) Mortality in adults with learning disabilities with and without a health check: a cohort study. The Lancet 394(2):27. https://doi.org/10.1016/S0140-6736(19)32824-7
28. Kennedy N, Kennedy J, Kerr M, Dredge S, Brophy S (2022) Health checks for adults with intellectual disability and association with survival rates: a linked electronic records matched cohort study in Wales, UK. BMJ Open 12(4):e049441. https://doi.org/10.1136/bmjopen-2021-049441
29. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G (2016) Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 15(10):1075–1088. https://doi.org/10.1016/s1474-4422(16)30158-2
30. Decouflé P, Autry A (2002) Increased mortality in children and adolescents with developmental disabilities. Paediatr Perinat Epidemiol 16(4):375–382. https://doi.org/10.1046/j.1365-3016.2002.00430.x
31. Nickels KC, Grossardt BR, Wirrell EC (2012) Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County. MN Epilepsia 53(12):2164–2171. https://doi.org/10.1111/j.1528-1167.2012.03661.x
32. Sillanpää M, Shinnar S (2010) Long-term mortality in childhood-onset epilepsy. N Engl J Med 363(26):2522–2529. https://doi.org/10.1056/NEJMoa0911610
33. Kiani R, Tyrer F, Jesu A et al (2014) Mortality from sudden unexpected death in epilepsy (SUDEP) in a cohort of adults with intellectual disability. J Intellect Disabil Res 58(6):508–520. https://doi.org/10.1111/jir.12047
34. Hesdorffer DC, Tomson T, Benn E et al (2011) Combined analysis of risk factors for SUDEP. Epilepsia 52(6):1150–1159. https://doi.org/10.1111/j.1528-1167.2010.02952.x
35. Shankar R, Jalihal V, Walker M et al (2014) A community study in Cornwall UK of sudden unexpected death in epilepsy (SUDEP) in a 9-year population sample. Seizure 23(5):382–385. https://doi.org/10.1016/j.seizure.2014.02.005
36. Tomson T, Surges R, Delamont R, Haywood S, Hesdorffer DC (2016) Who to target in sudden unexpected death in epilepsy prevention and how? Risk factors, biomarkers, and intervention study designs. Epilepsia 57(Suppl 1):4–16. https://doi.org/10.1111/epi.13234
37. Shankar R, Donner EJ, McLean B, Nashef L, Tomson T (2017) Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. Epileptic Disord 19(1):1–9. https://doi.org/10.1684/epd.2017.0891
38. Baxter H, Lowe K, Houston H, Jones G, Felce D, Kerr M (2006) Previously unidentified morbidity in patients with intellectual disability. Br J Gen Pract 56(523):93–98
39. Shankar R, Henley W, Boland C, Laugharne R, McLean BN, Newman C, Hanna J, Ashby S, Walker MC, Sander JW (2018) Decreasing the risk of sudden unexpected death in epilepsy: structured communication of risk factors for premature mortality in people with epilepsy. Eur J Neurol 25:1121–1127. https://doi.org/10.1111/ene.13651
40. Wagner AP, Croudace TJ, Bateman N et al (2017) Clinical services for adults with an intellectual disability and epilepsy: a comparison of management alternatives. PLoS ONE 12(7):e0180266. https://doi.org/10.1371/journal.pone.0180266