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Mortality in children with epilepsy: Cohort study using the clinical practice research datalink

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ABSTRACT

Objective: To estimate Mortality Rate (MR) in UK children with epilepsy (CWE) compared to children without epilepsy (CWOE), describe causes of death, determine Mortality Rate Ratios (MRRs) for cause-specific mortality, and to analyse the contribution of co-morbidities (respiratory disease, neoplasm, and congenital disorders) to mortality rate.

Method: Retrospective cohort study of children born between 1998 and 2017, using linked data from the Clinical Practice Research Datalink Gold (Set 18). Epilepsy diagnoses were identified using previously validated codes. Causes of death were defined as natural or non-natural. Epilepsy-related deaths in CWE were those where underlying or contributing cause of death was epilepsy, status epilepticus, seizures, ill-defined/unknown cause or sudden death. We used Cox proportional hazard analysis to investigate associations of epilepsy and mortality.

Results: There were 1,191,304 children followed for 13,994,916 person-years (median: 12) if which 9665 (0.8%) had epilepsy. Amongst CWE, 3.4% died. MR of CWE was 4.1 (95%CI 3.7–4.6)/1,000 person-years. CWE had an increased adjusted all-cause mortality (MRR 50.9,95%CI 44.8–57.7) compared to CWOE. Amongst the 330 deaths in CWE, 323 (98%) were natural, 7 (2%) non-natural, 80 (24%) epilepsy-related. MRR of non-natural deaths was 2.09 (95%CI 0.92,4.74, $p = 0.08$).

Significance: Amongst CWE, 3.4% died during the study period. All-cause mortality rate in CWE was 4/1,000 person-years representing a fifty-fold increased mortality risk, after taking into account sex and socioeconomic status, compared to similarly aged children who did not have epilepsy. Causes of death mostly were not seizure-related. Non-natural death in CWE was uncommon.

Key points

In this UK cohort, mortality rate in children with epilepsy was 4/1000 person-years.

The UK mortality rate in children with epilepsy was fifty times higher than children without epilepsy.

Most deaths were due to infections, respiratory causes and or related to underlying aetiology of epilepsy and not due to seizures

Non-natural death in children with epilepsy was uncommon.

1. Introduction

A large proportion of deaths in children are in those with chronic conditions, with chronic neurological conditions, including epilepsy, being the commonest [1]. Country-specific data on mortality in children with epilepsy (CWE) are most appropriate for best resource allocation because factors that influence mortality risk can vary between countries. These include underlying causes of epilepsy, socioeconomic status (SES) and variation in care and management of epilepsy [2]. Some deaths in CWE are unavoidable, but others may relate to deficiencies in the care received by children and their families [2,3]. Improvements in diagnosis, care and management of CWE may lead to reduction in potentially preventable deaths including sudden unexpected death in epilepsy (SUDEP), health care resource utilisation, and cognitive, emotional and behavioural problems ([2,4-6]).

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The mortality rate in CWE aged up to 17 years with mean follow-up of 10–16 years in Holland, Minnesota, and Connecticut ranges from 2.7–3.5/1000 person-years) [7–10]. Pooled analysis of these cohort studies and a Canadian cohort study found a mortality rate (MR) of 2.3/1000 person-years and a mortality rate ratio (MRR) of 4–8.5 times that of the general population of people aged 1–29 without epilepsy [11]. A Danish cohort study with data that included children and young adults up to age 30 years found a lower mortality rate of 0.4/1000 person years but with a higher MRR of 15, reflecting a much lower mortality rate in children without epilepsy in Denmark compared to the pooled cohort [12]. There are few UK studies on mortality in CWE.

A cohort study in England and Wales restricted to CWE who had been prescribed antiseizure medication (ASM) found a MR almost 2.5 times higher (5.6 per 1000 person-years) and 2.5 to almost 6 times higher MRR (22.4) for CWE compared to the pooled cohort above [13]. Being biased towards more severe epilepsies is one plausible explanation but the six times higher MRR could reflect a lower mortality rate in children without epilepsy in England and Wales compared to people aged 1–29 in areas that made up the pooled cohort. There have been two national UK, prospective, population-based active surveillance studies on mortality in CWE. One, with data from June 1, 2012 to 31 March 2013, identified 46 deaths in 10 months [2] whilst the more recent study with data from November 2016 to November 2017 showed an increase to 88 deaths in one year [14] suggesting a possible increasing mortality in CWE over time. However, as both used non-compulsory surveillance there was risk of underreporting, and neither had a comparator group. Thus, the contemporary MR and MRR in UK CWE compared to that of CWOE is uncertain. Given decreasing mortality in the UK childhood population [15]. we hypothesised MRR of CWE would be higher than previously reported.

Both UK surveillance studies obtained details on causes of death through questionnaires completed by notifying neurologists or from detailed review of medical notes ([2,14]). In both, cause of death was epilepsy-related in 25–33% that is similar to the 19% reported in the combined cohort study above [11]. Non-natural cause of death (for example suicide, non-seizure-related accidents) were not reported in either of the two UK surveillance studies but was found in 7% of the much larger pooled cohort study, suggesting low occurrence of such causes. However, given the likelihood of missed cases in the UK surveillance studies, and an increased risk of non-natural deaths in adults with epilepsy [16], underestimation of non-natural deaths in UK CWE needs consideration.

Our objectives were to estimate MR in CWE compared to CWOE, describe proportions of deaths as natural or non-natural and whether epilepsy-related, to determine MRRs for cause-specific mortality, and to analyse the contribution of co-morbidities (respiratory disease, neoplasm, and congenital disorders) to mortality rate in CWE.

2. Materials and methods

The study is reported in accordance with the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement [17].

We used coded routinely collected electronic health records to carry out a retrospective cohort study using linked data from the Clinical Practice Research Datalink (CPRD), Gold (Set 18). CPRD collects anonymised patient data from 674 UK General Practices (GPs). In the UK, GPs are responsible for early check-ups and vaccinations starting at two months of age thereby minimising the chances of missing healthy children within the database. However, it would miss children who were in hospital from birth to death or died before being registered with a GP, such as children who died during the perinatal or neonatal period. There are 4.4 million active (alive, currently registered) patients whose data meet quality criteria for use in research. Seven percent of the UK population are included, is representative of the general population in age, sex and ethnicity, and has been used in more than 1000 studies [18]. Primary care data are linked to other health data to provide a longitudinal, representative UK population health dataset [19]. Our data set comprised primary care data up to June 2020, linked to hospitalization, mortality, and deprivation (Index of Multiple Deprivation (IMD)) records. IMD is an area-based index to classify socioeconomic status (SES); quintile 1 corresponds to highest SES [20]. Mortality and hospitalization records are coded using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) coding system(21); GP records are coded using the Read code system, version 2.

The cohort population comprised children born between 1998 and 2017. Due to data protection, exact birth date was not available; only birth month and or birth year were available. If birth month was available, mid-month was used as birth date; if birth year only was available, mid-year was used as birth date; if birth year was not available, the record was removed from further analysis. Thus, if a child had a birth year of 2010 and a birth month of May we defined birth date as mid-May 2010. If we found a birth year of 2010 only, we defined the birth date as mid-June 2010. Children were followed through their linked GP records from the first anniversary of their defined date of birth (first birthday) to their death or censoring at age 20/December 2018 or loss to follow-up. We adopted this conservative approach of follow-up from the first birthday rather than defined birth day to minimise the chances of children who had acute symptomatic seizures, febrile seizures and or other mimics of epilepsy being included as CWE [22].

Children were considered as having epilepsy from their first recorded diagnosis. Epilepsy diagnoses were identified from Read codes used in a previous validation study using GP data from The Health Improvement Network (THIN) [23] and were reviewed in that study by an author of the current (RC), a consultant paediatric neurologist. The positive predictive value (PPV) of epilepsy in children in THIN was 92%. A Welsh study used the same Read codes to validate epilepsy diagnoses in adults and children within the Welsh Secure Anonymised Information Linkage (SAIL) databank and found a sensitivity of 86% and specificity of 97% [24]. We were unable to directly validate epilepsy diagnoses because access to individual level records was not allowed. In CPRD, administrative data are obtained from primary care data just as for THIN, and the same READ codes are used in both. Thus, differences in validity of READ codes between CPRD and THIN is unlikely. Children who did not have an epilepsy diagnosis listed on either GP or hospital records but had an epilepsy-related code (R95–99 and I46.1) in any position on their Office for National Statistics (ONS)-recorded cause of death, were excluded from primary analysis of MR. We excluded such children from the primary analyses because they may have died before a GP-visit, they may have had acute symptomatic seizures rather than epilepsy, and because they had no observation time. We observed all children as non-exposed from their first birthday onwards until death or end of follow-up but when they were diagnosed with epilepsy, they moved into the exposed group at their first diagnosis and followed-up as exposed. Thus, children first diagnosed at death had no observation time. Causes of death were determined using ICD-10 codes [21] in the ONS mortality records and categorised as:

1. Natural if underlying cause of death was any code other than V01-Y98 (non-natural causes) [16].
2. Non-natural if underlying cause of death was any of unnatural death (V01-Y98), transport accidents (V01–99 or Y85), other accidents (W00–99, X00–39, X50–59, or Y86), accidental poisoning with medication (X40–44), any accidental poisoning (X40–49), intentional self-poisoning with medication (X60–64 or Y10–14), any intentional self-poisoning (X60–69 or Y10–19), other suicide (X70–84, Y87.0, Y87.2, or Y20–34), homicide (X85-Y09, Y33.9, or Y87.1), and iatrogenesis (Y40–84 or Y88). We included events of undetermined intent in suicide estimates because most of these deaths were likely due to suicide [16].
3. Epilepsy-related if underlying or contributing cause of death in CWE was G40 (epilepsy), G41 (status epilepticus), R56.8 (seizures),

R95-R99 (ill-defined and unknown causes of mortality), or I46 (sudden death)(25). Thus, epilepsy-related deaths could be natural or non-natural.

4. Non-epilepsy-related if cause of death was not epilepsy-related.

Covariates: We controlled for quintiles of IMD, sex and birth year

2.1. Statistical analyses

All data were managed using Microsoft SQL-server and analysed using R4.1 [26]

Baseline characteristics were reported as numerical and percentage frequencies, medians, or means.

We calculated mortality rate by dividing number of deaths by sum of person-years at risk.

Outside of diseases of the nervous system, we observed the relative frequency of underlying cause of death was highest in infections, neoplasms, diseases of the respiratory system and congenital malformations/deformations/chromosomal abnormalities. We therefore examined as subgroups of natural deaths, cause specific mortality for infections [27], neoplasms(21), respiratory disorders [28], and congenital malformations/chromosomal conditions.

We used Cox proportional hazard analyses to investigate associations of epilepsy with all death and cause-specific mortality, adjusting for birth year, sex and SES. Epilepsy was included as a time-dependant variable, with epilepsy-status changing at date of first diagnosis. We also used Cox proportional hazard analyses to investigate the associations of epilepsy and neoplasms/respiratory disease/congenital disorders with all death childhood mortality. In all analyses, epilepsy was included as time-dependant variable, with the epilepsy-status changing at the date of the first diagnosis. In the analysis of the mortality risk in children with epilepsy diagnosed with neoplasms or respiratory disease, these were added as second time-dependant variable at the time of their first diagnosis. If a child was first time diagnosed prior to their first birthday (for all congenital/chromosomal disorders) children were classified as exposed from the first day of observation (first birthday). Sex and IMD were included in every model as categorical variables. The best transformation of birth year was determined using fractional polynomials and was included as a continuous variable in models.

2.2. Ethics

CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data. The current study was approved by the CPRD Independent Scientific Advisory Committee ([ref 20]_046).

3. Results

Forty-five children who did not have an epilepsy diagnosis listed on GP/hospital records but who had an epilepsy-related code on their ONS-recorded cause of death, were excluded. The remaining cohort comprised 1191,304 children (608,263 male) followed for 13,994,916 person-years (median: 12, IQR: 8 to 16). Of these, 9665 (incidence=0.8%, 5232 male) were children with epilepsy, with a follow-up of 80,321 person-years.

There were 330 (3.4%) CWE and 990 (0.08%) CWOE who died. Median age of death in CWE and CWOE was similar (6 years). Median interval from epilepsy diagnosis to death in CWE was 3.9 (Interquartile range 1.3 – 7.7) years. MR of CWE was 4.1 (95%CI 3.7–4.6)/1000 person-years. Although the MR in CWE did not differ according to sex, MR was reduced in females compared to males in CWOE. CWE had an increased all-cause mortality (MRR 50.9, 95%CI 44.8–57.7) compared to CWOE after considering year of birth, sex, and SES (See Table 1).

Amongst the 330 deaths in CWE, 7 (2%) were non-natural, 323 (98%) were natural. Disclosure restrictions preclude providing further details on the seven non-natural. Eighty (24%) of the 330 deaths in CWE were epilepsy-related and 250 (76%) were non-epilepsy-related (see Table 2).

Table 1
Association of childhood epilepsy with all-cause mortality adjusting for birth year, sex, and SES.

Characteristic	MRR	95% CI	p-value
Birth Year	0.99	0.97,1.00	0.06
Epilepsy			
No	Reference	Reference	Reference
Yes	50.9	44.8, 57.7	<0.001
Sex			
Male	Reference	Reference	Reference
Female	0.83	0.75, 0.92	<0.001
IMD quintile			
1			
2	1.27	1.07, 1.50	0.007
3	1.27	1.07, 1.50	0.007
4	1.30	1.10, 1.54	0.002
5	1.54	1.31, 1.81	<0.001

MRR = Mortality Rate Ratio, CI = Confidence Interval.

No code for sudden unexpected unexplained death in epilepsy (SUDEP) was available during the study period but five (6.3%) of epilepsy-related deaths had a sudden death code as underlying or contributing recorded cause of death. Thirty-four (42%) of epilepsy-related death had epilepsy (G40) or status epilepticus (G41) or seizures (R56.8) as the underlying cause of death on their death certificates but the underlying cause of death in most cases was not due to seizures.

In CWOE 30% of deaths were non-natural and 70% were natural (see Table 2). After adjusting for birth year, sex and SES, compared to CWOE, CWE were at increased risk for natural death (MRR 70.2, 95%CI 61.5–80.0) including cause-specific death from infections (MRR141, 95%CI 95.4–209), neoplasms (12.6, 95%CI 8.1–19.7), respiratory disease (MRR 130, 95%CI 86.4–196), and congenital/chromosomal conditions (MRR 435, 95%CI 224–845). MRR of non-natural deaths was 2.1 (95%CI 0.92,4.74)

A varying proportion of the increased risk of deaths in children with epilepsy was related to the underlying comorbid conditions, not because of the epilepsy alone. Compared to children without epilepsy and without congenital disorder, children with epilepsy without congenital disorder had a 40 times higher mortality. After congenital disorder diagnosis, children without epilepsy had an 18 times higher mortality.

Table 2
Causes of death in children with epilepsy and children without epilepsy.

Causes		Epilepsy, N (% all deaths)	
		YES	NO
ALL		330	990
Natural		323 (97.8)	693 (70)
	Infections	45 (13.6)	74(7.5)
	Neoplasms	23 (7.0)	277 (28.0)
	Pulmonary Disease	40 (12.1)	65 (6.6)
	Congenital malformations/ chromosomal conditions	23 (7.0)	16 (1.6)
	Other (epilepsy, other conditions/diseases of the nervous system, conditions/diseases not of the nervous system)	192 (59.4)	261 (37.6)
Non-natural		7 (2.2)	297 (30)
Epilepsy-Related		80 (24)	–
Non-Epilepsy-Related		250 (76)	–

Children with both congenital disorder diagnosis and epilepsy had a 153 times higher mortality. Similarly, children with epilepsy without a neoplasm had 50 times increased mortality, children with a neoplasm but no epilepsy had 264 times higher mortality but those having both epilepsy and neoplasm had 513 times increased mortality. Finally, children with epilepsy who never had a recorded diagnosis of respiratory disease had 48 times higher mortality, but if there was a diagnosis of epilepsy and respiratory disease, mortality was 29 times; the confidence intervals of these point estimates overlapped (see Table 3).

4. Discussion

The main findings from this retrospective cohort, linkage study are that in CWE: [1] 3.4% died giving a Mortality Rate of 4.1 (95%CI 3.7–4.6)/1000 person-years; [2] there was increased all-cause adjusted MRR (50.9, 95%CI 44.8–57.7) compared to CWOE and this was higher than previously reported; [3] the majority of deaths were from natural causes with only 2% due to non-natural causes; [4] twenty four percent were coded as epilepsy-related of which 6% were coded as a sudden death on their death certificates. In most cases cause of death was not seizures but infections, respiratory causes, and or related to underlying aetiology.

Higher MRs have been reported in people with epilepsy (up to 15.8/1000 person-years) but these have been in studies with markedly different study design (for example, using pooled data from adults and children and inclusion of only a single epilepsy syndrome associated with drug-resistant seizures) to our study ([29,30]). Herein we compare our findings to those of Dutch, North American and Danish studies in which we acknowledge there are some differences in the data collection methods and samples sizes to our study, but their methodologies were similar to ours, although not exactly matching.

The MR in CWE in the current study was higher than the 2.3/1000 person-years reported amongst CWE in the pooled Dutch and North American cohort study(11). Given the study period of the combined cohort was earlier, advances in epilepsy management worldwide since then, and 0.4/1000 person-years lower mortality rate in Danish CWE in a more recent study, it was disappointing to find such a high mortality rate in CWE in the current study. Since we were only able to include children from their first birthday, we speculate that part of our observed high MR was due to an increase in the number of children who would have previously died without epilepsy during infancy. Such children may have survived beyond their first birthday due to improvement in perinatal care and immunisations but would then have increased likelihood for disabilities and or epilepsy thereby increasing their risk for premature mortality during childhood or early adulthood [25]. The starkness of high MR in the current study was pronounced when put in the context that it was fifty times that compared to that of the general UK childhood population. This MRR is more than double the MRR of twenty-two in an earlier UK study a decade ago(13), 6–12 times that of the pooled Dutch-American cohort study(11), and 3.5 times that of the Danish study(12). Since differences in MR between studies were not of those multiplicities, the MRR in our study is at least partly in keeping with denominator differences between studies; UK childhood mortality rates have steadily decreased from 33/100,000 in 1981 to 7.0/100,000 in 2020 [15]. This decreased general childhood mortality would have been due to improvements in antenatal, perinatal and early life care [31] but such improvements would be less likely to have an impact on mortality risk in CWE, which are more related to aetiology, management/treatment, and comorbidties of epilepsy.

The current study found that most deaths in CWE were not epilepsy-related which was similar to that previously reported [11]. Our findings of nearly a quarter of deaths were epilepsy-related (due to the epilepsy itself, its treatment, or comorbidities worsened by epilepsy [32] was similar to that of the UK-wide review of epilepsy deaths in CWE that involved comprehensive assessment of medical records [2]. Whilst our study lacked detailed granularity of longitudinal care of CWE leading up to their death and circumstances surrounding deaths afforded by the review, findings from both suggest that future research is needed into whether improvement in quality of care of CWE could decrease mortality risk. Potentially modifiable factors identified from the UK-wide review included fragmentation of care, and recognition of and response to acute illness in CWE [2]. Genetic testing can aid in identifying aetiology of the epilepsies and aid in rationalisation and optimisation of treatments [33], and should therefore be encouraged.

The UK review of deaths in CWE coincided with the second round of the national Epilepsy12 audit. Epilepsy12 was established in 2009 and has the continued aim of helping epilepsy services and those who commission health services, to measure and improve quality of care for CWE(2). Improvement in some areas of epilepsy service between rounds have been demonstrated including more CWE having input from a paediatrician with expertise in epilepsy. However, management of CWE, including during admission to hospital, will not always be by experts in epilepsy and thus more widespread understanding of management of epilepsy amongst all clinicians taking care of CWE is needed [34]. Our results suggest that if increased mortality risk was related to lack of sufficient care of CWE, the changes in practice as a result of Epilepsy 12 have yet to have any impact on mortality risk.

Although there were seven non-natural deaths (2% of all deaths) in CWE in our study, this contrasts to zero in recent UK surveillance studies and seven percent found in the combined cohort study on deaths in CWE ([2,11,14]). Both UK surveillance studies had follow-up for less than a year, but the combined cohort study had long follow-up as the current. We found no statistically significant difference in the likelihood of death due to non-natural causes in CWE compared to CWOE. Together these results suggest that unlike in adults with epilepsy [16], non-natural death in CWE in middle/high income countries is not common but there remains merit in physicians and parents/carers minimising the risk through strategies such as ensuring close supervision whilst CWE are swimming. A substantial concern in cause of death studies is that SUDEP and seizure-related deaths can be missed. It could be argued that would be less of a problem in children where there tends to be close supervision by carers/parents. Bearing in mind variations in co-sleeping practices within families, events that occur during sleep in particular could be unwitnessed and or unexplained and increase the likelihood of post-mortem determination of cause of death. During the study period, a specific ICD code for SUDEP did not exist but we found five (6.3%) epilepsy-related deaths had a sudden death code in any position on the recorded cause of death. This is similar to the seven percent found in a 40-year follow-up study investigating childhood-onset epilepsy [35] but much lower than the 36% in a Swedish study [36]. In the Swedish study,

Table 3
Association of epilepsy and congenital/chromosomal disorders, neoplasms and respiratory disease with all-cause mortality, after adjusting for birth year, sex, and socioeconomic status.

Characteristic	MRR	95% CI	p-value
No epilepsy, no congenital/chromosomal disorder	Reference	Reference	Reference
Epilepsy, no congenital/chromosomal disorder	39.5	34.1, 45.7	<0.001
Congenital/chromosomal disorder, no epilepsy	17.6	13.6, 22.7	<0.001
Congenital/chromosomal disorder and epilepsy	152.9	69.6, 331.9	<0.001
No epilepsy, no neoplasm	Reference	Reference	Reference
Epilepsy, no neoplasm	48.6	42.4, 55.8	<0.001
Neoplasm, no epilepsy	264	217, 321	<0.001
Neoplasm and epilepsy	513.2	184, 1612	<0.001
No epilepsy, no respiratory disease	Reference	Reference	Reference
Epilepsy, no respiratory disease	48.4	42.1, 55.6	<0.001
Respiratory disease, no epilepsy	1.5	1.21, 1.84	<0.001
Respiratory disease and epilepsy	29.0	13.2, 68.7	<0.001

MRR = Mortality Rate Ratio, CI = Confidence Interval.

epilepsy was mentioned on the death certificate in only 63% of SUDEP cases [36]. It is possible that our reliance on death certificate information and lack of a specific code resulted in underestimation of SUDEP.

In the current study 24% of CWE had epilepsy-related deaths, and data from the latest round of Epilepsy 12 audit in 2021 show that only 53% of CWE have evidence of receiving information on SUDEP [37]. Thus, there is scope for clinicians and health organisations to improve on information giving on risk factors and interventions for reducing epilepsy-related death, including SUDEP, such as ASM adherence and nocturnal supervision as recommended in national guidelines for the management of CWE ([38,39]). Adjusting for birth year, sex and socioeconomic status, we assessed the association of epilepsy and three categories of comorbidity (congenital/chromosomal disorder, neoplasm, respiratory disease) with all-cause mortality. Looking across all three categories, the individual MRR for children with epilepsy but without congenital/chromosomal disorder, or neoplasm or a respiratory condition ranged from 40 to 49, suggesting that the effect of epilepsy on its own on mortality was quite substantial. The comorbidities on their own were also associated with increased mortality since the MRR children without epilepsy ranged from 2–264. The risk of mortality when there was epilepsy plus comorbidity depended on the type of comorbidity. Children with epilepsy and congenital/chromosomal disorder or neoplasm had markedly increased mortality risk (MRR 153 and 513 respectively) than those without such comorbidities. This was perhaps unsurprising since children with epilepsy and congenital/chromosomal disorders are more likely to have structural brain malformations and or dysfunction. Those with neoplasms could have primary or secondary brain tumours. The lower MRR point estimate for children with epilepsy and a respiratory disorder compared to without was not statistically significant and thus, limited any inference. We recommend that CWE with congenital/chromosomal disorder/neoplasm/respiratory disease have their epilepsy managed by a paediatrician with expertise in epilepsy.

The main strength of this study was use of data from the CPRD Gold database, a large, established, and well utilised primary care database in the UK [40], with extensive validation [18]. We were able to adjust for potential confounding factors and we had a long follow-up period. The 0.8% incidence of CWE in the current study was similar to that reported in other high-income countries and provides external validation of epilepsy diagnoses in CPRD [41]. However, there are limitations.

4.1. Limitations

Epilepsy diagnoses in the UK are, according to The National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network guidelines, to be made by physicians with expertise in epilepsy. It was not possible to be sure whether diagnoses were made by such, and we were unable to directly validate epilepsy diagnoses. However, we used an approach that has been shown to have the highest positive predictive value when using administrative data to identify people with epilepsy in epidemiological research [42]. Nonetheless, we could still have missed CWE who were not given an epilepsy code. Epilepsy mortality is relatively high in early infancy. The data source only allowed us to follow-up children from their first birthday and given the high incidence of epilepsy in infancy [43], we may have missed some CWE who died during their first year of life. Had we been able to follow-up from actual date of birth and validate epilepsy diagnoses directly, our mortality estimate could possibly have been higher.

We did not have details of the epilepsy type, syndrome, severity, or overall management and as such, were not able to determine epilepsy risk factors that may increase mortality risk in CWE. The retrospective nature of the study limited detailed understanding of the temporal relationship of circumstances surrounding death. We used information from death certificates and concerns over the variation in the degree of accuracy on clinician-provided cause of death on death certificates have long been debated. For example, attribution of mortality to respiratory cause as compared to epilepsy can be challenging, because a seizure could contribute to an aspiration pneumonia. Alternatively, epilepsy with a comorbidity of cerebral palsy and developmental disability could contribute to pressure ulcers, urinary tract infections, gastrostomy tube infections, or tracheostomy related infections. Results may not be generalisable to other countries, even those with similar medical services.

We were unable to estimate a standardised mortality rate (SMR) as we did not have age-specific mortality rates for CWE in our study, nor age-sex structure of the general UK population corresponding to the age-range for our study population of 1–20 years. For indirect standardisation, mortality rate on the general population of children aged 1–20 years was not available; mortality rate was only available for those children aged 1–15 years. Using the UK age 1–15 population would result in an indirect SMR of 55.

5. Conclusion

In this cohort study, 3.4% of CWE died during the study period. All-cause mortality rate in CWE was 4/1000 person-years, representing a fifty-fold increased risk compared to similarly aged children in the UK who do not have epilepsy after taking into account sex and SES. A quarter of deaths were epilepsy-related but the cause of death in most CWE was not seizure-related but due to infections, respiratory causes or the underlying aetiology of the epilepsy. Unlike in adults, non-natural death in children with epilepsy was uncommon.

Author's contributions

RFC conceptualised the study and assisted in study design, data analyses, data interpretation and writing of the manuscript. CS carried out data analyses, and assisted in study design, data interpretation and writing of the manuscript.

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Accessibility to the protocol, raw data and programming code

Accessibility to the raw data is by application directly to CPRD. Access to the protocol and programming codes is on application to the corresponding author

Declaration of competing interest

Neither author has any conflict of interest to disclose.

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