Risk of unnatural mortality in people with epilepsy

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Key Points

Question: What is the risk of cause-specific unnatural mortality in people with epilepsy and what is the contribution of medication to these deaths?

Findings: People with epilepsy, identified from the general population, are at three-fold increased risk of any unnatural mortality compared to those without. A five-fold increased risk was observed for accidental medication poisoning. Psychotropic medication and opioids were the medication groups most commonly used in poisoning deaths, not antiepileptic drugs.

Meaning: Clinicians should provide advice on accident and suicide prevention and consider toxicity of concomitant medication when prescribing for people with epilepsy.

Abstract

Importance: People with epilepsy are at increased risk of mortality, but the cause-specific risks of all unnatural causes have not been reported.

Objective: Estimate cause-specific unnatural mortality risks in people with epilepsy, and identify the medication types involved in poisoning deaths.

Design: Cohort studies in two electronic primary care datasets, linked to hospitalization and mortality records. Each person with epilepsy was matched to up to twenty individuals without epilepsy on age (+/-2 years), gender and general practice.

Setting: The Clinical Practice Research Datalink (CPRD) in England (01/01/1998-31/03/2014) and the Secure Anonymised Information Linkage (SAIL) Databank in Wales (01/01/2001-31/12/2014).

Participants: We identified 44,678 (CPRD) and 14,051 (SAIL Databank) individuals in the prevalent epilepsy cohorts and 891,429 (CPRD) and 279,365 (SAIL Databank) individuals in the comparison cohorts.

Exposure: People with epilepsy were identified from primary care epilepsy diagnoses and associated antiepileptic drug (AED) prescriptions.

Main Outcomes and Measures: Unnatural mortality was coded by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes V01-Y98 in Office for National Statistics (ONS) mortality records. We estimated hazard ratios in each dataset using stratified-Cox proportional hazards models and meta-analysed these using the DerSimonian and Laird random effects

model. The frequency at which each medication type was involved was estimated as a percentage of all medication poisoning deaths.

Results: People with epilepsy were more likely to die from any unnatural cause (HR, 2.77, 95%CI 2.43-3.16), accident (HR, 2.97, 95%CI, 2.54-3.48) or suicide (HR, 2.15, 95%CI 1.51-3.07) than the comparison cohort. We observed particularly large risk elevations for accidental medication poisoning (HR, 4.99, 95%CI 3.22-7.74) and intentional self-poisoning with medication (HR, 3.55, 95%CI 1.01-12.53). Opioids (56.5%, 95%CI 43.3%-69.0%) and psychotropic medication (32.3%, 95%CI 20.9%-45.3%) were more commonly involved in poisoning deaths among people with epilepsy than antiepileptic drugs (9.7%, 95%CI 3.6%-19.9%).

Conclusions and Relevance: People with epilepsy are at increased risk of unnatural death versus people without epilepsy. They should be adequately advised about accident prevention and monitored for suicidal ideation, thoughts and behaviours. The suitability and toxicity of concomitant medication should be considered when prescribing for comorbid conditions.

Introduction

People diagnosed with epilepsy are two-to-three times more likely to die prematurely compared to the rest of the population. The degree to which this risk is elevated varies by cause of death.[1, 2] Earlier research has focused on sudden unexpected death in epilepsy (SUDEP), with less attention paid to other causes. A recent 'Call for Action' identified the need to better understand cause-specific mortality risk, particularly for unnatural causes (i.e. accident, suicide, homicide and iatrogenic effects), in people with epilepsy.[3] Furthermore, the need for accurate identification of epilepsy and cause of death in epidemiologic studies, has been emphasized.[4]

Several secondary care-based observational studies have reported two-to-five fold increased risks of unnatural mortality.[1, 5, 6] Some examined risk by type of accident,[5, 6] one reported method of suicide in people with epilepsy,[7] but none comprehensively reported risks across the full range of suicide and accident types. A previous study of suicide from the US National Violent Death Reporting System reported that antiepileptic drugs (AEDs) were taken in just 6% of intentional poisoning deaths in epilepsy.[7] This contrasts with a study of non-fatal self-poisoning, where AEDs were the most commonly taken medication type in people with epilepsy (27%).[8]

We aimed to estimate relative risks of specific causes of unnatural mortality in people with epilepsy versus a matched comparison cohort without epilepsy. We utilized two linked primary care-mortality databases to accurately estimate risks of cause-specific unnatural mortality. We also examined how frequently specific types of medication were involved in medication poisoning deaths.

Methods

Design, Setting and Participants

We conducted two population-based cohort studies in the (1) Clinical Practice Research Datalink (CPRD) and the (2) Secure Anonymised Information Linkage (SAIL) Databank. The CPRD is a general practice database which covers approximately 7% of the UK population. It contains anonymized patient-level data including demographics, diagnoses, test results and prescribed treatments.[9] We used the July 2015 release, which included 13,979,404 patients whose data was deemed to be of acceptable research quality standards, from 689 practices. It is deemed representative of the age, gender and ethnicity distributions of the UK population.[9] We identified the epilepsy and comparison cohorts from a subset of practices whose anonymized patient data were linked to the following additional data sources: Office for National Statistics (ONS) mortality records, Index of Multiple Deprivation (IMD) 2010 and Hospital Episode Statistics (HES). These sources provide information on cause of death, quintiles of deprivation based on the patient's postcode and inpatient hospitalizations, respectively.[9] All of the linked practices were in England and comprised 74% of the English practices in the CPRD.

The SAIL Databank contains data from 13 health and social care databases in Wales. Data from individuals is anonymously linked between databases though a unique identifier.[10] The general practice dataset (GPD) contains diagnostic, treatment and test data from 360 (76%) of general practices in Wales (n=4,052,388).[11] Hospital admission diagnoses and discharge dates are detailed in the Patient Episode Database for Wales (PEDW). The Annual District Death Extract (ADDE) provides ONS data on date and cause of death.[12] There was no overlap

between the practices included in the CPRD and the SAIL Databank cohorts because none of the Welsh practices in the CPRD were in the subset eligible for data linkage.

The Independent Scientific Advisory Committee (ISAC) of the Medicine and Healthcare Regulatory Agency (MHRA) approved access to the CPRD and linked data (protocol 15_046RA2R). Approval was granted to access the SAIL Databank from the Information Governance Review Panel (IGRP), an independent body consisting of a range of government, regulatory and professional agencies, which oversees study approvals in line with ethical permissions already granted for conducting data analysis in the SAIL Databank (approval number 0204).[10,13] Informed consent is not required for use of these anonymised datasets. This study is reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement.[14]

The International League against Epilepsy (ILAE) recommend the presence of both a diagnostic code for epilepsy and an AED treatment code for reliable ascertainment of epilepsy in epidemiologic studies.[15] We therefore adopted this definition. Epilepsy diagnoses are recorded in the CPRD and the GPD using the Read code system version 2.[16] Code lists were produced by searching for epilepsy-related terms in the CPRD medical dictionary. This list was refined following discussion with a neurologist and in comparison with studies previously conducted in the CPRD[17, 18] and the SAIL Databank.[19] A list of AEDs licensed in the UK was produced by one pharmacist (HCG) and checked by another (DMA), based on drugs listed in the British National Formulary (BNF 68).[20]

We defined the epilepsy index date as the latest date at which a person had received both an epilepsy diagnostic code plus an associated AED prescription. The AED prescription could be issued in the month before or up to 6 months after the date of the diagnostic code. We required the index date to be within the study periods, which we defined based on corresponding linkage availability. This was 01/01/1998-03/31/2014 for the CPRD and 01/01/2001-12/31/2014 for the SAIL Databank. Follow-up began on the index date which occurred after registration of the patient in a practice. Separately in the CPRD and SAIL Databank, we matched people with epilepsy to up to 20 individuals who had never received a diagnostic code for epilepsy and were alive on the date that follow-up began (online material). We matched these comparison cohorts to their respective epilepsy cohorts on gender, year of birth (+/- 2 years) and general practice (Figure 1). Members of the comparison cohorts were followed up from the same day as the individual they were matched to in the epilepsy cohort.

We followed the epilepsy and comparison cohorts until the earliest date of: death; transfer out of the practice; end of data collection from the practice; or study end. In the SAIL Databank, it was possible to follow patients who transferred to other practices.

We identified diagnoses and treatments using general practice data. We used published Read code lists to identify patients diagnosed with a range of mental illnesses.[21, 22] Our code lists for migraine, neuropathic pain and substance misuse were verified by two General Practitioners and are available along with the epilepsy and AED codes at www.ClinicalCodes.org.[23] Hospital discharge diagnoses were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) coding system.[24]

Cause-specific Mortality Outcomes

We determined cause of death from the ONS-recorded underlying cause of death, as coded by ICD-10. We used the following codes to identify unnatural death (V01-Y98): transport accidents (V01-99, Y85), other accidents (W00-99, X00-39, X50-59, Y86), accidental poisoning with medication (X40-44), any accidental poisoning (X40-49), intentional self-poisoning with medication (X60-64, Y10-14), any intentional self-poisoning (X60-69, Y15-19), other suicide (X70-84, Y20-34, *excluding Y33·9)*, homicide (X85-Y09, Y33·9, Y87·1) and iatrogenic effects (Y40-84, Y88). We included events of undetermined intent in suicide estimates as per UK convention, because most of these deaths are likely to be suicides.[25] We identified specific types of medication involved in poisoning deaths according to codes T36-50 in supplementary causes of death fields (eTable 1).

Statistical Analysis

We applied a common protocol to conduct separate analyses in the two databases using Stata version 13 (StataCorp,College Station,Texas). Baseline characteristics were reported as numerical and percentage frequencies, medians or means and compared using Student's t-tests, Mann-Whitney U tests or Chi-squared tests, as appropriate. We examined the proportion of individuals per cohort with mental health diagnoses, neuropathic pain or migraine, before or after cohort entry. We calculated mortality rates by dividing the number of events by the sum of person-years at risk. We accounted for the matched design by fitting stratified-Cox proportional hazards models to estimate unadjusted and adjusted hazard ratios for specific causes of death. Proportionality assumptions were checked using a test for Schoenfeld residuals and visually by graphical inspection. Adjustments were made for area-level

deprivation because people with epilepsy are known to reside in more deprived areas than those without,[19] which may independently increase risk of death. Deprivation was recorded by quintiles using the Index of Multiple Deprivation (IMD-2010) in CPRD and the Welsh Index of Multiple Deprivation (WIMD) in the SAIL Databank. Where level of deprivation was missing, individuals were assigned to an 'unknown' category.

We meta-analyzed the hazard ratios estimated from each dataset using the DerSimonian and Laird random effects model implemented via the *metan* command in Stata.[26] Additionally, we restricted the cohorts to the incident epilepsy and comparison cohorts and estimated risks for the four main subgroups (all-cause mortality, unnatural death, accident and suicide). The purpose of this sensitivity analysis was to explore whether there was evidence of survival bias in using the prevalent cohort for our primary analysis. We also produced Kaplan-Meier survival estimates for all unnatural death separately for the two datasets, accounting for competing risks. The frequency of involvement of each medication type in poisoning deaths were pooled across the CPRD and SAIL Databank and reported as percentages of all poisoning deaths for the prevalent cohorts.

Results

We matched 44,678 people with epilepsy to 891,429 persons without epilepsy in the CPRD and 14,051 people with epilepsy to 279,365 individuals without epilepsy in the SAIL Databank (Figure 1). The baseline characteristics are described in Table 1. In both datasets, 51% of the epilepsy and comparison cohorts were male. The median age on entry was 40 (IQR 25-60) in the CPRD and was 43 (IQR 24-64) in the SAIL Databank. With the exception of neuropathic pain, people with epilepsy were more

likely to have been diagnosed with any of the comorbid conditions examined at baseline, to have been treated with psychotropic medication, and to have higher levels of deprivation, than the comparison cohort ($p<0.05$). People with epilepsy were also more likely have recorded a new mental illnesses diagnosis during follow-up. The comparison cohorts had longer follow-up than the epilepsy cohort (CPRD 5.1 vs. 4.0 years; SAIL Databank 7.7 vs. 6.9 years), and follow-up ended more commonly due to death in the epilepsy cohorts (CPRD 14.7% vs 7.1%; SAIL Databank 15.3% vs 8.4%).

Counts and rates for each unnatural cause of death are presented separately for the two datasets in Table 2. The meta-analyzed hazard ratios for cause-specific unnatural mortality, adjusted for area-level deprivation, are presented in Figure 2. These estimates were similar to the unadjusted estimates. Compared to persons without the condition, people with epilepsy were at an increased risk of unnatural mortality (deprivation-adjusted HR 2.77, 95% CI, 2.43-3.16). We observed this elevated risk for both accidental death (deprivation-adjusted HR 2.97, 95% CI, 2.54-3.48), which represented the majority of unnatural deaths (Table 2), and suicide (deprivation-adjusted HR 2.15, 95% CI, 1.51-3.07). The pooled relative risks for homicide (deprivation-adjusted HR 3.51, 95%CI, 1.16-10.57) and iatrogenic fatalities (deprivation-adjusted HR 4.77, 95%CI, 2.47-9.22) were also elevated, albeit with wide confidence intervals for these exceptionally rare causes of death.

Pooled across the two databases, 22.8% (95%CI, 18.0-28.3%) of unnatural deaths were medication poisonings in the epilepsy cohorts compared to 11.2% (95%CI, 10.0-12.6%) in the comparison cohorts. The medication types most commonly taken in poisoning deaths were opioids (epilepsy cohorts 56.5%, 95%CI, 43.3-69.0%; comparison cohorts 47.3%, 95%CI, 41.4-53.3%) and psychotropic medication

(epilepsy cohorts 32.3%, 95%CI, 20.9-45.3%; comparison cohorts 36.7%, 95%CI, 31.0-42.6%). By contrast, AEDs were taken in relatively few medication poisoning deaths (epilepsy cohort 9.7%, 95%CI 3.6-19.9%; comparison cohort 2.5%, 95%CI, 1.0-5.1%).

Sensitivity analysis identified 14,057 people with incident epilepsy and 263,610 in the comparison cohort in the CPRD, and 7,274 people with incident epilepsy and 144,287 in the comparison cohort in the SAIL Databank. The hazard ratios estimated from meta-analysis of the incident cohorts were similar to those estimated from the prevalent cohorts (Figure 3). The cause-specific survival rate after five years were 99.7% (95%CI 99.5%-99.8%) and 99.8% (99.8%-99.8%) for the epilepsy and comparison cohorts respectively in the CPRD; and 99.5% (95%CI 99.3%-99.7%) and 99.8% (95%CI 99.8%-99.8%), in the SAIL Databank (eFigure 1, eFigure 2).

Discussion

Across two linked-primary care and mortality databases, people with epilepsy had increased risk of all types of unnatural mortality compared to those without epilepsy. In both people with epilepsy and a matched comparison cohort, psychotropic medication and opioids were the medicine groups most commonly used in poisoning deaths, with AEDs much less frequently reported. To our knowledge, this is the first study to comprehensively examine cause-specific unnatural mortality risks, including both accidental and intentional medication poisoning separately, in people with epilepsy.

Our relative estimates for all unnatural death, accidental death and suicide, are in the same direction, but generally lower, than those recorded in studies conducted using secondary care records.[5, 6, 27] Fazel et al. observed an odds ratio of 3.6 (95% CI, 3.3-

4.0) for all external injury, 3.5 (95% C,I 3.3-4.2) for suicide and 3.6 (95% CI 3.1-4.1) for accident.[5] Christensen et al. also reported a slightly higher risk of suicide (RR 3.17, 95%CI 2.88-3.50).[27] Standardized mortality ratios (SMR) of 5.6 (95% CI 5.0-6.3) for injury and poisoning, and 3.5 (95% CI 2.6-4.6) for suicide, were reported by Nilsson et al.[6] These studies defined epilepsy populations from hospital records,[5, 6, 27] most of which comprised inpatient episodes with some outpatient coverage.[5, 6] Therefore, it is possible that only individuals with more severe epilepsy were included. By using two primary care datasets, we have demonstrated that increased risks extend to people with epilepsy in the community. Only one other study has estimated the specific risk of accidental poisoning. The reported odds ratio (5.1, 95%CI, 3.9-6.5)[6] was similar to our meta-analyzed estimate.

Reasons for the increased risk of accidental death may include direct consequences of seizures[3] or be unrelated to epilepsy. The mental illness comorbidities associated with epilepsy are also associated with increased risk of accident[28] and suicide.[29] Indeed we saw greater proportions of people in the epilepsy cohort with mental health diagnoses at baseline and during follow-up, than the comparison cohort. There have been suggestions that suicidality and epilepsy share common neurological pathways,[30] which could explain the increased risk of suicide. Clinicians should explore any symptoms of mental illness in people with epilepsy, and ask about thoughts of taking own life. Additionally, the psychosocial impact and stigma surrounding epilepsy may contribute to risk.[31] It is possible that stigma or presence of comorbid mental illness explains much of the three-fold elevation in homicide risk that we observed, an estimate congruent with that reported from a Swedish registry study (adjusted-OR 2.8, 95%CI 1.6-4.8).[5]

The elevated risks identified for poisoning deaths might be attributable to the accessibility of medication in people with epilepsy, both AEDs and medication prescribed to treat comorbidities. The ease of access to means to take one's own life strongly influences suicide risk.[32] However, AEDs were relatively infrequently recorded as being taken in accidental and intentional poisoning deaths among people with epilepsy. Our estimate that AEDs were taken in a tenth of poisonings is similar to Tian et al, who reported AED involvement in six percent of suicides among people with epilepsy.[7] Many of the AEDs taken may have a lower relative toxicity than psychotropic drugs and opioids. This may have changed over time due to a reduction in use in phenobarbital,[33] which historically contributed to over half of AED poisonings.[34, 35] However, AEDs are frequently involved in non-fatal self-harm.[8] Ongoing vigilance is required to monitor nonfatal self-harm and poisoning deaths, as trends in AED prescribing change. ONS records report increasing involvement of gabapentin and pregabalin in poisoning deaths.[36] This has been largely attributed to the diversion of pregabalin and gabapentin for recreational use.[37] As these AEDs are commonly used for treating conditions other than epilepsy, their involvement could extend beyond people with epilepsy.

Our study meets the ILAE recommendations for defining epilepsy[15] and classifying mortality by cause[4] in epidemiologic studies. A major strength of our investigation is that we examined two large, linked, nationally representative primary care datasets. Our outcomes were identified from ONS mortality statistics, which is the most accurate method of ascertaining cause of death. These primary care datasets encompassed the whole spectrum of epilepsy, without restriction to more severe cases as in hospital-based cohorts. We applied a common study protocol across both datasets, to enable meta-analysis of relative risks even where observed event

counts were small. The elevated risk of intentional self-poisoning that was observed in the meta-analysis would not have been detected by utilizing only the SAIL Databank. Additionally, we verified our main findings by comparison with an incident epilepsy cohort.

We are aware of potential limitations common to research using routinely collected data to investigate outcomes such as suicide. Firstly, the datasets are not generated primarily for the purpose of conducting research, and residual confounding may therefore be present. Secondly, some suicides may have been misclassified. We accounted for this by including unnatural deaths of undetermined intent in our suicide definition. However, coroners in England and Wales have more frequently been using narrative verdicts to describe likely suicides in recent years, rather than assigning a specific verdict.[38] Some of our meta-analyzed estimates were of low precision, due to the small event counts for the rarest cause-specific mortality outcomes. For this reason, we could not estimate risks for specific subgroups of unnatural death in the incident epilepsy cohort. We were unable to report the medication involvement for each dataset independently without compromising anonymity. Additionally, we could not subdivide the medications beyond that deducible from ICD-10 ‘T’ codes.

In summary, we have demonstrated that people with epilepsy have elevated risks for most specific causes of unnatural death, including accidental and intentional poisoning by medication. Further research is needed to identify suitable measures to mitigate these risks. In the meantime, clinicians should be aware of the elevated unnatural mortality risks and should carefully monitor patients accordingly. AEDs seemingly play a minor role in poisoning deaths, with psychotropic drugs and opioids more often involved. Therefore, when prescribing to people with epilepsy, the

potential for poisoning and associated relative toxicity of concomitantly prescribed medication should be considered in light of the elevated fatal poisoning risk in this population.

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Disclosures of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

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Table 1. Characteristics of epilepsy and comparison cohorts

Characteristics	CPRD		SAIL
	Epilepsy cohort (n=44,678)	**Comparison cohort (n=891,429)**	**Epilepsy cohort (n=14,051)**
Male	22,961 (51.4%)	458,008 (51.4%)	7,716 (51.1%)
Median age on entry (IQR)	41 (25-60)	40 (25-60)	44 (24-62)
Level of deprivation[a]			
1 least deprived	7,621 (17.0%)	178,850 (20.1%)	2,202 (15.7%)
2	8,878 (19.9%)	194,644 (21.8%)	2,314 (16.4%)
3	8,565 (19.2%)	178,281 (20.0%)	3,059 (21.8%)
4	9,723 (21.8%)	179,831 (20.2%)	2,997 (21.3%)
5 most deprived	9,826 (22.0)	158,696 (17.8%)	3,468 (24.7%)
Missing	65 (0.1%)	1,127 (0.1%)	11 (0.1%)
Previous Diagnoses			
Alcohol misuse[a]	2,682 (6.0%)	12,056 (1.4%)	936 (6.7%)
Anxiety[a]	7,195 (16.1%)	104,532 (11.7%)	2,452 (17.5%)
Bipolar disorder[a]	465 (1.0%)	3,293 (0.4%)	143 (1.0%)
Depression[a]	9,096 (20.4%)	123,989(13.9%)	2,930 (20.9%)
Eating disorder[a]	548 (1.2%)	5,849 (0.7%)	183 (1.3%)
Migraine[a]	3,081 (6.9%)	46,150 (5.2%)	1,058 (7.5%)
Neuropathic pain	1,578 (3.5%)	30,763 (3.5%)	961 (6.8%)
Personality disorder[a]	836 (1.9%)	3,675 (0.4%)	307 (2.2%)
Schizophrenia[a]	1,273 (2.9%)	6,711 (0.8%)	377 (2.7%)
Self-harm[a]	3,563 (8.0%)	23,248 (2.6%)	1,050 (7.5%)
Substance misuse[a]	2,972 (6.7%)	11,923 (1.3%)	1,122 (8.0%)
Prior prescription at baseline			
Antidepressant[a]	11,175 (25.0%)	171,866 (19.3%)	4,043 (28.8%)
Antipsychotic[a]	6,823 (15.3%)	88,433 (9.9%)	1,843 (13.1%)
Anxiolytic/hypnotic[a]	14,562 (32.6%)	124,898 (14.0%)	4,938 (35.1%)
Lithium[a]	162 (0.4%)	1,982 (0.2%)	61 (0.4%)
Opioid[a,b]	14,355 (32.1%)	252,308 (28.3%)	6,603 (47.0%)
Follow up			
Median follow-up time[a]	4.0 (IQR 1.4-8.4)	5.1 (IQR 2.1-9.3)	6.9 (2.9-10.3)

Table 1. Characteristics of epilepsy and comparison cohorts continued

Characteristics	CPRD		SAIL
	Epilepsy cohort (n=44,678)	Comparison cohort (n=891,429)	Epilepsy cohort (n=14,051)
New diagnoses during follow-up			
Alcohol misuse[a]	784 (1.8%)	9,321 (1.1%)	296 (2.1%)
Anxiety[a]	2,901 (6.5%)	45,429 (5.1%)	1,069 (7.6%)
Bipolar disorder[a]	204 (0.5%)	1,595 (0.2%)	69 (0.5%)
Depression[a]	2,858 (6.4%)	46,189 (5.2%)	1,081 (7.7%)
Eating disorder[a]	383 (0.9%)	3,796 (0.4%)	176 (1.3%)
Migraine	975 (2.2%)	17,155 (1.9%)	331 (2.4%)
Neuropathic pain	1,217 (2.7%)	23,349 (2.6%)	729 (5.2%)
Personality disorder[a]	212 (0.5%)	963 (0.1%)	92 (0.7%)
Schizophrenia[a]	465 (1.0%)	2,861 (0.3%)	213 (1.5%)
Self-harm[a]	846 (1.9%)	6,497 (0.7%)	322 (2.3%)
Substance misuse[a]	1,913 (4.3%)	25,016 (2.8%)	315 (2.2%)
Reason for end of follow-up[a]			
Death identified from ONS	6,599 (14.8%)	62,903 (7.1%)	2,143 (15.3%)
Practice stopped contributing	7,175 (16.0%)	170,882 (19.1%)	6,330 (45.0%)
Study end	16,623 (37.2%)	403,717 (45.3%)	5,578 (39.7%)
Patient transferred out of practice	14,281 (32.0%)	253,927 (28.5%)	N/A

[a]significant ($p<0.05$) difference between epilepsy and comparison cohorts [b]includes single prescriptions of opioids for a
8mg/500mg

Cause of death	CPRD								
	Epilepsy (n=44,687; PYs=232,095)			Comparison cohort (n=891,429; PYs=5,272,571)			Epilepsy cohort (n=14,051; PYs=93,9		
	Number	rate / 100,000 PYs	95% CI	Number	rate/ 100,000 PYs	95% CI	Number	rate/ 100,000 PYs	95
All deaths	6,559	2826.0	2758.0-2895.2	62,903	1193.0	1183.7-1202.3	2,143	2280.5	21 2
Natural	6,406	2760.0	2692.9-2828.5	61,127	1159.3	1151.0-1168.6	2,065	2197.5	21 2
Unnatural	193	83.1	71.8-95.8	1,776	33.7	32.1-35.3	78	83.0	6 1
Accident	134	57.7	48.4-68.4	1,279	24.3	23.0-25.6	58	61.7	46
Transport accident	13	5.6	3.0-9.6	225	4.3	3.7-4.9	8	8.5	3.
Other accident	93	40.7	32.3-49.1	936	17.8	16.6-18.9	41	43.6	31
Accidental medicine poisoning	24	10.3	6.6-15.4	90	1.7	1.4-2.1	8	8.5	3.
All accidental poisoning	28	12.1	8.0-17.4	118	2.2	1.9-2.7	9	9.6	4.
Suicide	47	20.3	14.9-26.9	407	7.7	7.0-8.5	16	17.0	9.
Suicide poisoning with medication	26	11.2	7.3-16.4	80	1.5	1.2-1.9	<5	N/A	
All suicide poisoning	26	11.2	7.3-16.4	100	1.9	1.5-2.3	<5	N/A	
Other suicide	21	9.1	5.6-13.8	307	5.8	5.2-6.5	12	12.8	6.6
Homicide	<5	N/A	N/A	18	0.3	0.2-0.5	<5	N/A	
Iatrogenic	9	3.9	1.8-7.4	72	1.4	1.1-1.7	<5	N/A	

Table 2. Event counts and mortality rates for cause-specific unnatural mortality in prevalent epilepsy

Figure 1. Flow diagram showing delineation of epilepsy and comparison cohorts. The identifi
comparison cohorts from the SAIL Databank and the CPRD. Individuals who did not meet the coho
excluded at certain stages of cohort construction.

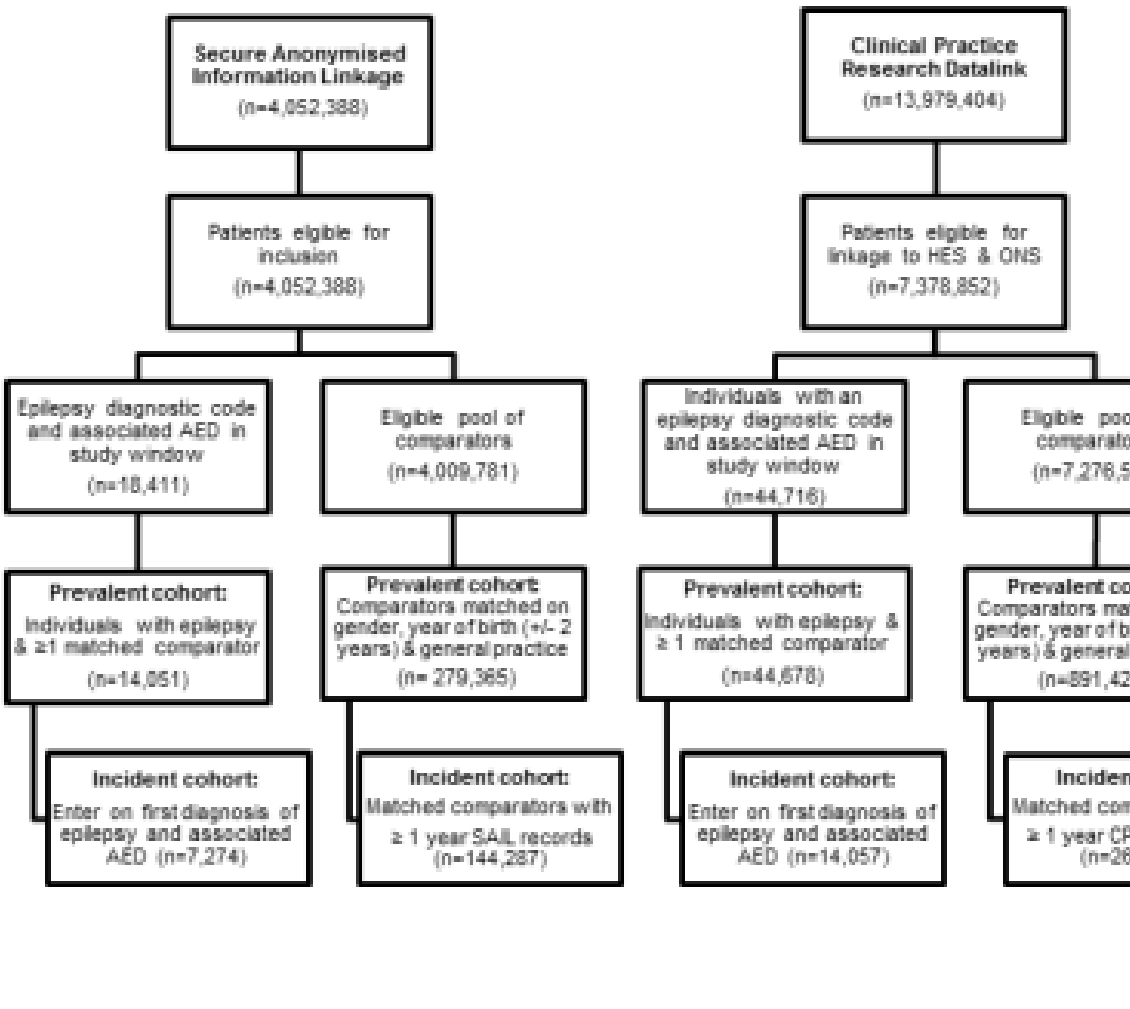


Figure 2. Forest plot showing deprivation-adjusted hazard ratios for cause-specific unnatural mortality. Deprivation-adjusted hazard-ratios, for cause-specific mortality in the prevalent epilepsy cohort versus comparison cohort. Hazard ratios were estimated separately in the CPRD and SAIL and meta-analyzed using the DerSimonian and Laird random effects model.

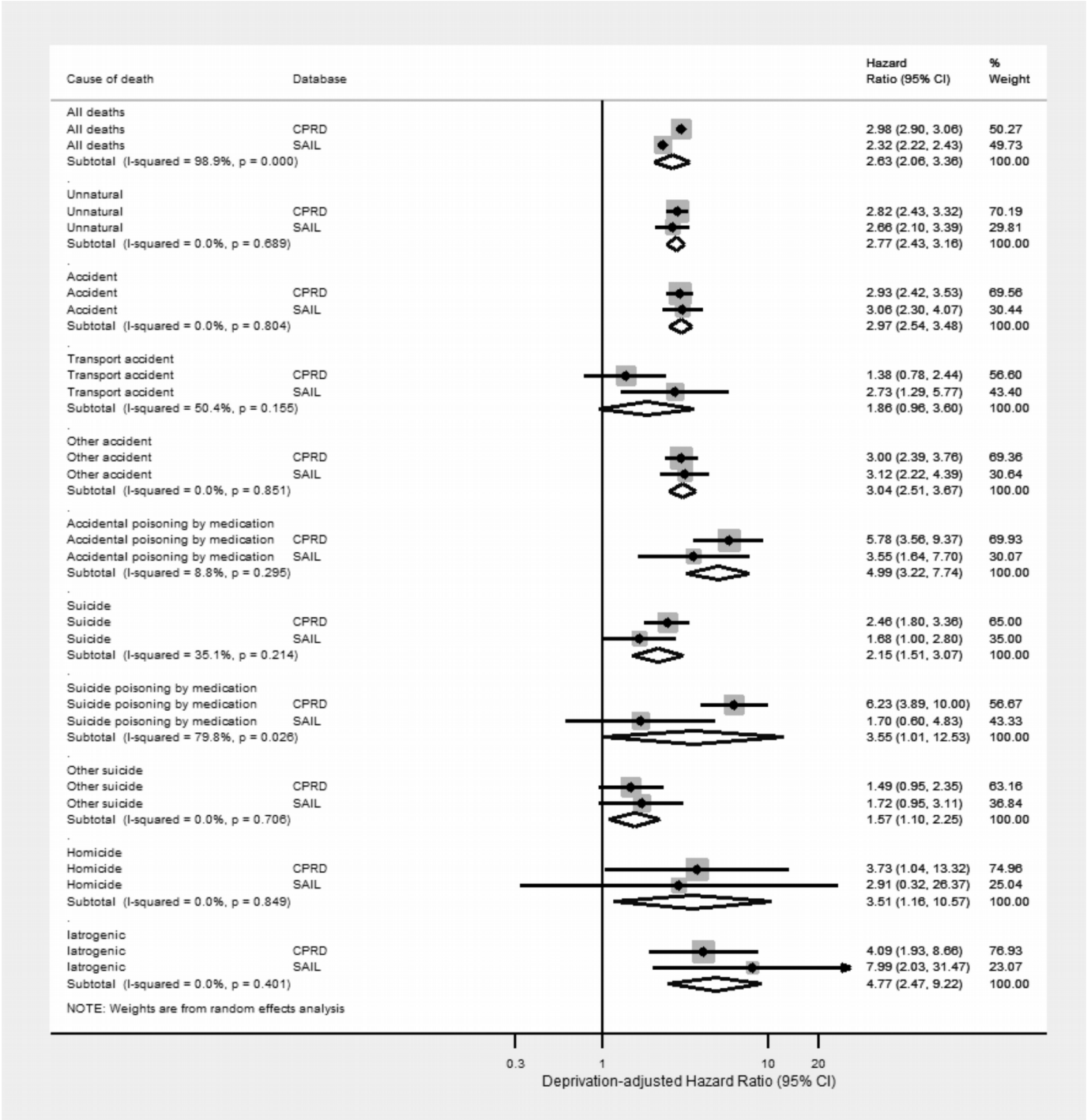
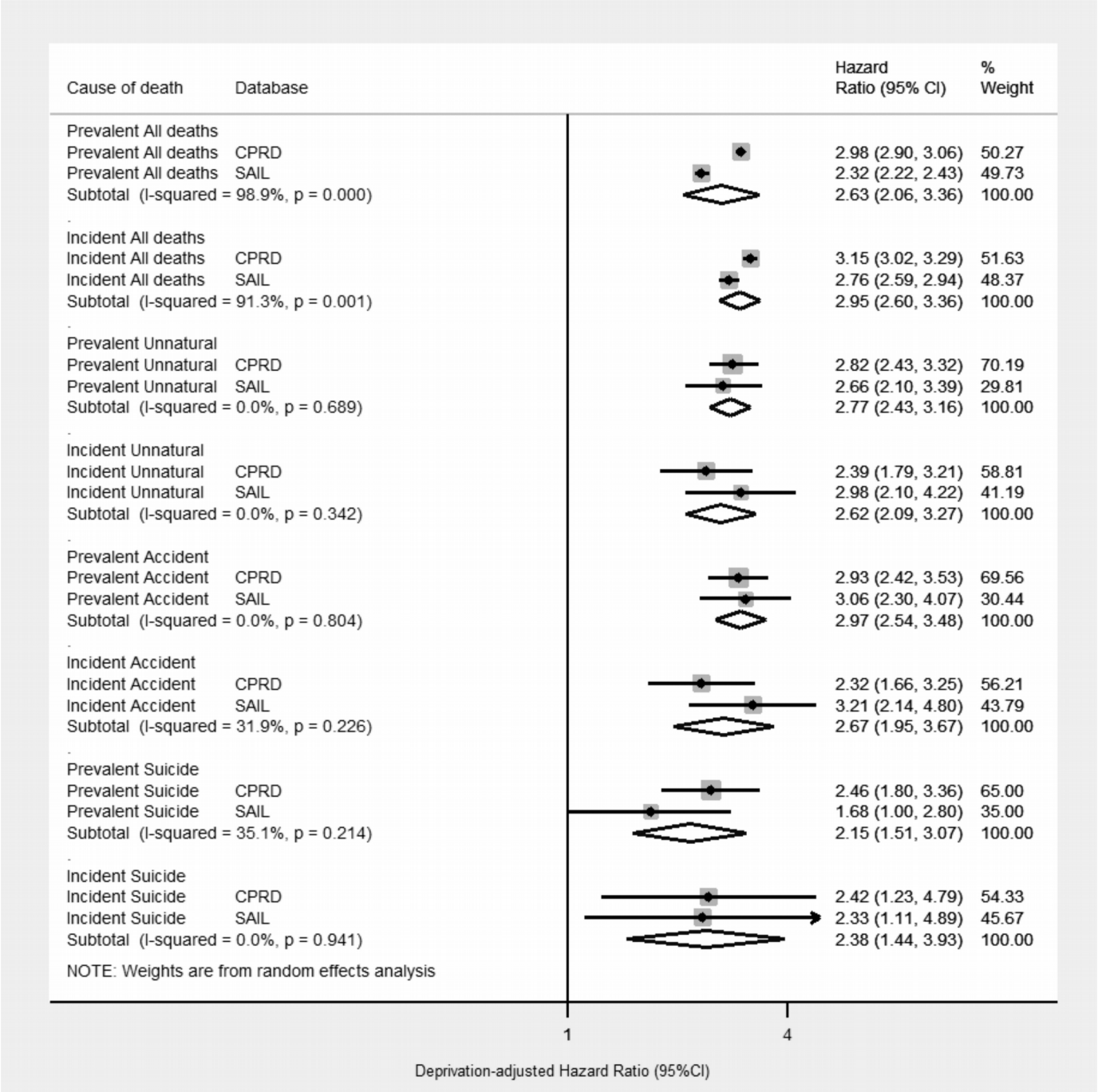


Figure 3. Forest plot showing deprivation-adjusted hazard ratios estimated from prevalent and incident epilepsy cohorts. Deprivation-adjusted hazard ratios for all deaths, unnatural death, accidental death and suicide are shown for prevalent and incident epilepsy cohort, versus comparison cohorts. Hazard ratios were estimated separately in the CPRD and SAIL and meta-analyzed using the DerSimonian and Laird random effects model.



Online Material. Risk of unnatural mortality in people with epilepsy

Hayley C Gorton, Roger T Webb, Matthew J Carr, Marcos del Pozo Baños, Ann John, Darren M Ashcroft

Explanation of the matching process applied to delineate the matched-cohort study

Separately in the CPRD and the SAIL Databank, people with epilepsy were matched to up to 20 individuals who had never received a diagnostic code for epilepsy and were alive on the date that follow-up began. They were matched on gender, year of birth (+/-2 years) and registered general practice; and followed up from the same day as the corresponding individual in the epilepsy cohort. We employed an algorithm that used nearest-neighbor matching. Individuals were ineligible for inclusion in the comparison cohort if they ever had a diagnostic code for epilepsy. In both the epilepsy and comparison cohorts, at least one day of follow-up after the entry date was required. The matching ratio of up to 20:1 was used to improve statistical power to detect rare outcomes, in line with evidence reported by Hennessy et al. that there are benefits to increasing the matching ratio for case-control studies above 5:1 when the exposure prevalence is low among control subjects. (1) Therefore, an increased matching ratio will be beneficial for the matched cohort design when incidence is very low in the comparison cohort. It enables more precise estimation of relative risks for exceptionally rare specific causes of death such as homicide. Whilst this matching ratio was desired, in practice it was not possible to match all individuals with epilepsy to 20 people. This was because there were not enough individuals who were the same gender, had the same year of birth (+/- 2 years), were registered in the same general practice and who had never had a diagnosis of epilepsy. Each individual was matched to as many individuals as possible who satisfied the matching criteria. In the CPRD there was a median of 19 (IQR 18-19) individuals in the comparison cohort for each individual in the epilepsy cohort. The median was 20 (IQR 20-20) in the SAIL Databank.

Reference:

i) Hennessy S, Bilker WB, Berlin JA, Strom BL. Factors influencing the optimal control-to-case ratio in matched case–control studies. Am J Epidemiol. 1999;149(5):489.

e-Table 1. ICD-10 codes used to classify medication taken in fatal poisonings

Medication Group	Codes
Psychotropic medication	T40.5, T40.7, T40.8, T40.9, T42.4, T43.0-9, T50.5
Opioid	T40.0-4, T40.6
Non-opioid	T39
Antiepileptic Drugs	T42.0-3, T42.5-7
Other	T36-38,T41,T42.8,T44-49,T50.0-4, T50.6-9

ICD-10 codes listed in supplementary cause of death fields in the ONS mortality record

Figure e-1. Kaplan-Meier plot depicting probability of cause-specific survival in relation to unnatural mortality in the CPRD

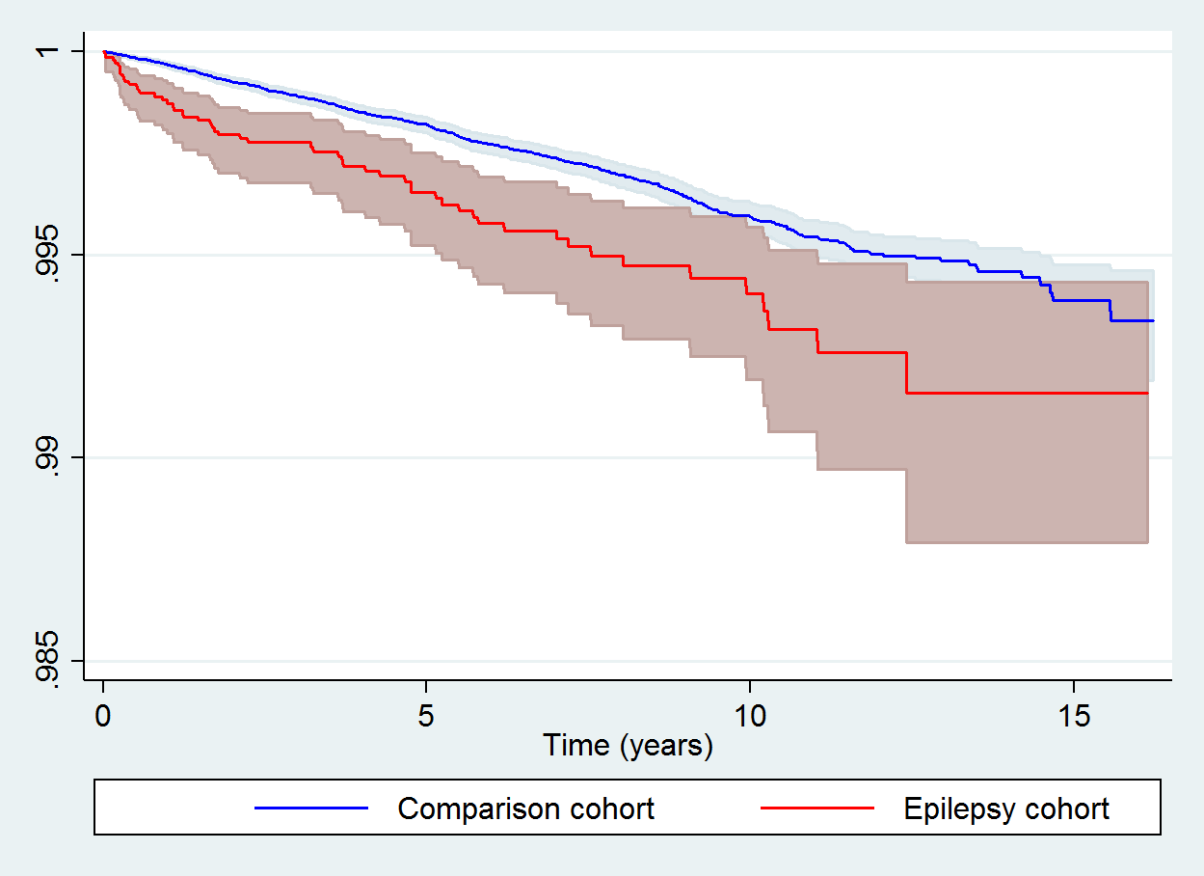


Figure e-2. Kaplan-Meier plot depicting probability of cause-specific survival in relation to unnatural mortality in the SAIL Databank