

# Under-reporting of sudden unexpected death in epilepsy\*

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**ABSTRACT – Aims.** The identification and characterization of sudden unexpected deaths in epilepsy (SUDEP) may be improved, helping to optimize prevention and intervention. We set out to assess the frequency and demographic and clinical characteristics of SUDEP cases in a sudden death cohort. **Methods.** All out-of-hospital deaths were investigated from March 1, 2013 to February 28, 2015 in Wake County, NC, attended by the Emergency Medical Services. Cases were screened and adjudicated by three physicians to identify sudden death cases from any cause among free-living adults, aged 18-64. In total, 399 sudden death victims were identified during this two-year period. Seizure history, demographic and clinical characteristics, and healthcare utilization patterns were assessed from death records, emergency response scene reports, and medical records. Sudden death cases with a history of seizures were summarized by an experienced chart abstractor (SC) and adjudicated by an experienced neurologist (OD). We then compared demographic and clinical characteristics and healthcare utilization patterns of neurologist-identified SUDEP cases to other sudden death victims in our population-based registry of sudden death from any cause. **Results.** SUDEP accounted for 5.3% of sudden deaths. However, seizures or complications of seizures were only considered the primary cause of death on death certificates in 1.5% of sudden deaths. SUDEP cases were more likely to have a history of alcohol abuse. Mental health disorders and a low level of medication compliance and healthcare utilization were common among SUDEP victims.

**Conclusions.** SUDEP accounts for approximately 5.3% of sudden deaths from any cause in individuals aged between 18 and 64. Death certificates underestimate the burden of sudden death in epilepsy, attributing only 1.5% of sudden deaths to seizures or complications of seizures. Accurate documentation of epileptic disorders on death certificates is essential for the surveillance of SUDEP. Further, interventions that promote better use of medical services and patient engagement with healthy living practices may reduce sudden deaths in epilepsy.

**Key words:** SUDEP, case ascertainment, underestimation

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In the United States, 3.4 millions people have active epilepsy (Zack and Kobau, 2017). Epilepsy can be fatal through the direct effect of seizures (e.g. sudden unexpected death in epilepsy [SUDEP], drowning, status epilepticus, motor vehicle accidents, falls, burns) or indirect effects of epilepsy and its treatment (e.g. suicide, obesity, and cardiovascular effects of antiepileptic drugs [AEDs]). While SUDEP has been recognized for more than a century, knowledge regarding incidence and risk factors is lacking. SUDEP is a concern for primary care physicians and neurologists, as people with epilepsy have a 24-27-fold higher sudden death mortality rate than the general population (Devinsky *et al.*, 2015). However, the SUDEP incidence varies depending on criteria and definitions, research data source, and epilepsy population (Tomson *et al.*, 2008). Compounding the problem, standard methods for case ascertainment, such as death certificates, under-report such deaths (Bell *et al.*, 2004; Atherton *et al.*, 2017).

Risk factors for SUDEP include increased frequency of seizures (especially tonic-clonic seizures), younger age at onset of epilepsy, longer duration of disease, lack of AED treatment, and AED polypharmacy (Hesdorffer *et al.*, 2011). The role of specific medications, such as lamotrigine, remains controversial (Aurlen *et al.*, 2011, Tomson *et al.*, 2012). According to the Epilepsy Foundation, optimal management of seizures (*i.e.* AEDs, the ketogenic or modified Atkins diet, respective surgery, and neuromodulation), living a healthy lifestyle, and regular follow-ups with specialists may reduce the risk of SUDEP. However, there is limited information on the underlying associations and potential population risk factors of these sudden deaths. To address these gaps, we studied the incidence of SUDEP using a population-based cohort of sudden death and assessed the demographic and clinical characteristics of SUDEP victims as well as their healthcare utilization patterns.

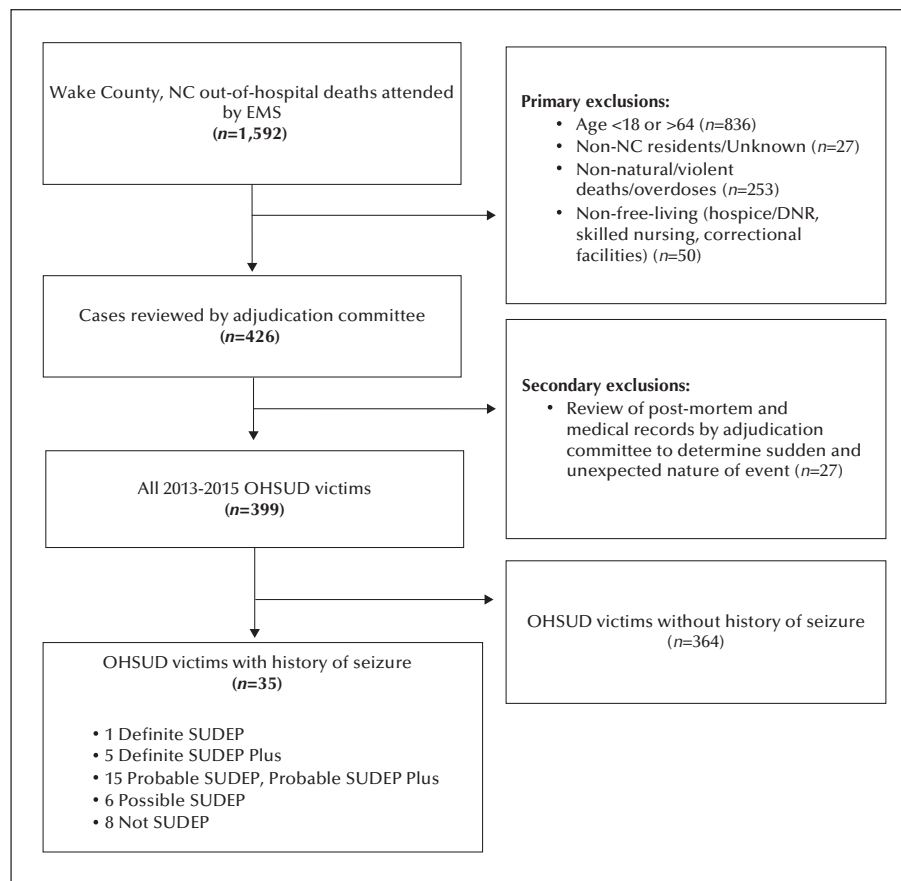
## Research design and methods

The pilot phase of the Sudden Unexpected Death in North Carolina (SUDDEN) project involves the study of out-of-hospital, natural deaths attended by the Emergency Medical Services (EMS) in Wake County, North Carolina (NC) between March 1, 2013 and February 28, 2015 (Nanavati *et al.*, 2014; Lewis *et al.*, 2016; Mounsey *et al.*, 2017). Wake County is a predominantly urban region (population size: 974,289) in central NC with Raleigh as the major city. During the study period, there were 15,151 deaths in Wake County. A preliminary screening of EMS scene reports was completed to identify deaths among non-institutionalized adults aged 18-64, who resided in

NC. Medical records for all subjects were rigorously pursued. Records were requested from the death certificate signer ("death attendant") and three major hospitals in the Wake County area. For participants without a physician death certificate, reports were requested from the NC Medical Examiner's office. The records obtained were subsequently reviewed to determine whether the subject received additional treatment from other providers, and requests were sent to these providers. If no records were received after 30 days of the initial request, a follow-up call was placed to the provider (Nanavati *et al.*, 2014). After obtaining medical records from hospitals and providers and post-mortem examinations, all medical records were manually chart-abstracted and extensively reviewed to exclude a non-sudden cause of death including traumas, homicide or suicide, end-stage cancer, or overdose based on post-mortem examination and clinical records. Cases were considered overdoses if there were three or more toxic drug levels or one lethal level of a drug on the toxicology report based on reference values defined by the NC Office of the Chief Medical Examiner Toxicology Laboratory. The death certificate cause of death was not used to determine cause of death for adjudication purposes. This process was completed by two trained research assistants, followed by majority adjudication by three cardiologists not affiliated with the study. To ensure quality control, 15% of all cases were reviewed (*figure 1*).

Records for up to five years before death were manually chart-abstracted to determine medical conditions, including seizure disorder. Seizure disorder included physician-documented epilepsy, alcohol-withdrawal seizures, cerebral palsy, a mention of seizure disorder on the medical examiner report or autopsy, and otherwise specified seizure disorders, excluding history of isolated seizure and isolated seizure at the time of death.

For cases with a history of seizures, data was summarised by an experienced chart abstractor (SC) and reviewed by a neurologist (OD) with expertise in epilepsy-related mortality. These cases were classified as Definite, Probable, Possible, and Not SUDEP based on criteria established by Nashef *et al.* (2012). Definite SUDEP is a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for seizure and documented status epilepticus (seizure duration  $\geq 30$  minutes or seizures without recovery in between), in which post-mortem examination does not reveal a cause of death. Definite SUDEP Plus satisfies the definition of Definite SUDEP: if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to combined



**Figure 1.** Ascertainment of Out-of-Hospital Sudden Unexpected Death (OHSUD) victims.

effects of both conditions, and if autopsy or direct observations/recordings of the terminal event did not prove the concomitant condition to be the cause of death. Probable SUDEP and Probable SUDEP Plus have the same definition as SUDEP, however, these former terms are used in the absence of autopsy and describe a victim who died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death. Possible SUDEP is defined by the presence of a competing cause of death. A case is Not SUDEP if a clear cause of death is known (Nashef *et al.*, 2012).

In this study, Definite, Definite Plus, and Probable SUDEP were considered SUDEP cases. Demographic and clinical characteristics and healthcare utilization were compared between SUDEP and non-SUDEP cases. Healthcare encounters were documented for two years before death and were categorized as outpatient clinic visits, Emergency Department visits, and other visits including hospitalisations, surgeries, wound care, procedures, and home visits. Census tracts were determined based on the US Census Geocoder using the subject's home address.

Additional information about each census tract was obtained from the Federal Financial Institutions Examination Council Geocoding and Mapping System. Demographic and clinical characteristics were summarised using frequencies for categorical variables and mean (SD) for continuous variables. Analysis of variance and two-tailed chi-square tests were used to compare demographic and clinical characteristics between groups. Results were considered statistically significant for  $p < 0.05$ .

### Ethics

This project was reviewed by the University of North Carolina's institutional review board and found to be exempt (study #: 13- 2445). The project was given expedited review because it was deemed low risk and safeguards for confidentiality were deemed appropriate. This IRB is reviewed annually. Furthermore, the ethical compliance of study procedures and analyses is monitored by an internal ethics committee.

## Results

### Frequency of SUDEP

Of the 399 adjudicated sudden death cases, 35 had a history of seizure (9%). Among those with a history of seizure, one case was considered Definite SUDEP (3%), five cases Definite SUDEP Plus (14%), 15 cases Probable or Probable SUDEP Plus (43%), six cases Possible SUDEP (17%), and eight cases Not SUDEP (23%).

### Demographics and clinical characteristics

Table 1 summarizes the demographics and clinical characteristics of SUDEP cases and non-SUDEP cases. Demographic characteristics did not differ significantly between groups. Alcohol abuse was more common in SUDEP victims (47.6% vs 20.6%;  $p=0.01$ ) (figure 2). No other clinical differences were found between groups.

### Healthcare utilization

There were no significant differences in the average number of total healthcare encounters or the types of encounters for two years per patient between groups. SUDEP victims averaged 1.90 visits over two years, and non-SUDEP victims averaged 5.23 visits (figure 3). Outpatient clinic visits constituted the majority of encounters in both groups, and ED encounters made up 8-9% of the encounters. There were no documented neurology visits in the two years prior to death among 21 SUDEP victims.

### SUDEP victims

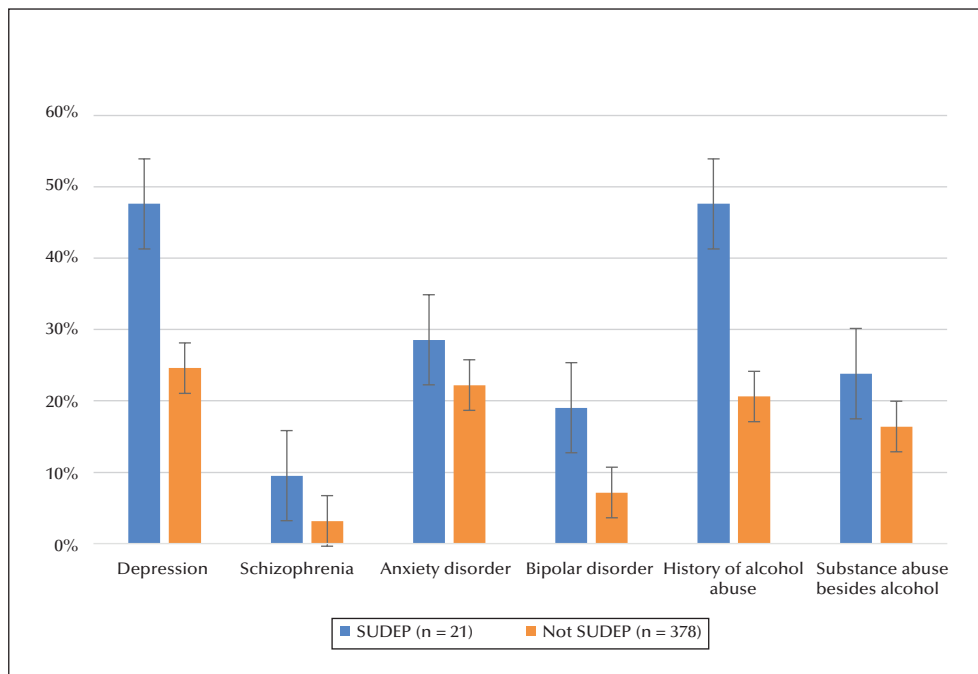
Among 35 sudden death victims with a history of seizure, 21 (60%) met the criteria for Definite or Probable SUDEP. This accounted for 5.3% of all sudden death cases. "Seizures" or "complications of seizures" was listed as the primary cause of death on physical death certificates in six sudden death cases (1.5%). The sensitivity of death certificates was 28.6% (95% CI: 11.3%-52.2%). Two additional cases listed cerebral palsy as a contributory cause of death. In no cases was SUDEP explicitly documented as the cause of death, and the sudden nature of death was never indicated. Among the 15 additional neurologist-identified SUDEP cases not identified by death certificate, the cause of death was documented as cardiac ( $n=6$ ; four with cardiac arrest, one with acute MI, and one with hypertensive arteriosclerotic cardiovascular disease), alcohol poisoning (one patient), respiratory failure (one patient), cerebrovascular accident (one patient), frontotemporal dementia (one patient), pulmonary embolism (one patient), aspiration (one

**Table 1.** Demographic and clinical characteristics of SUDEP vs non-SUDEP among victims of sudden death from any cause ( $n=399$ ).

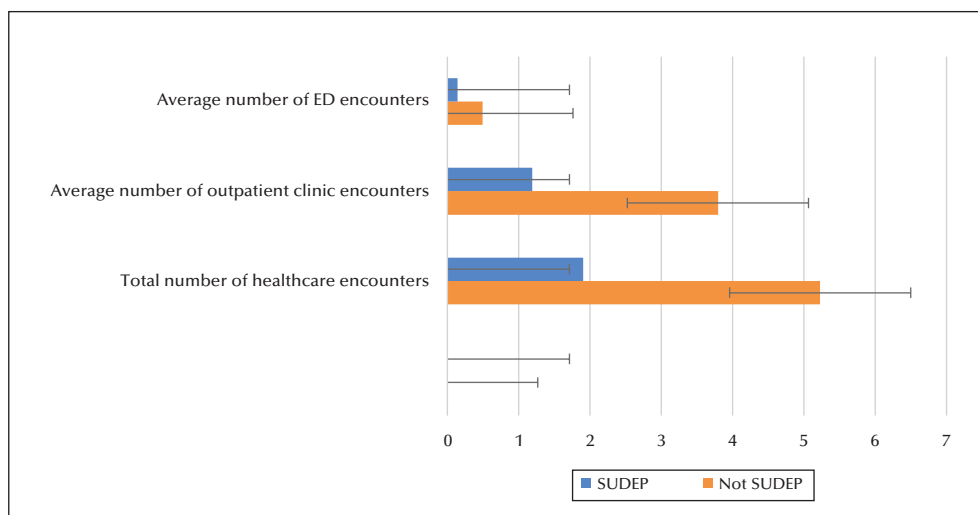
	SUDEP ( $n=21$ )	Not SUDEP ( $n=378$ )
	$n$ (%)	$n$ (%)
<b>Age</b>		
Q1, Q3	46, 61	48.25, 60
Median	53	55
Male	11 (52%)	262 (69%)
White	12 (57%)	237 (63%)
Married	5 (24%)	143 (38%)
<b>Education level</b>		
<12 years	3 (14%)	52 (14%)
12 years	7 (33%)	126 (33%)
13-15 years	4 (19%)	101 (27%)
$\geq 16$ years	6 (29%)	94 (25%)
Unknown	1 (5%)	5 (1%)
<b>Circumstance of death</b>		
Unwitnessed death	19 (90%)	339 (90%)
Medical examiner death attendant	8 (38%)	192 (51%)
<b>Clinical characteristics</b>		
BMI (average, [SD])	27.9 (6.5)	30.8 (9.0)
History of smoking	7 (33%)	166 (44%)
<b>Comorbidities</b>		
Heart failure	0 (0%)	51 (13%)
Coronary artery disease	3 (14%)	91 (24%)
History of hypertension	8 (38%)	216 (57%)
Diabetes mellitus	2 (10%)	107 (28%)
Dyslipidaemia	4 (19%)	142 (38%)
Stroke history	1 (5%)	25 (7%)
Chronic kidney disease	0 (0%)	44 (12%)
Chronic respiratory disorder	5 (24%)	118 (31%)
Metabolic syndrome	2 (10%)	90 (24%)

patient), asthma (one patient), and neoplasm (two patients).

Among SUDEP victims, prior histories included cerebral palsy (two patients), stroke (one patient), and traumatic brain injury (two patients). Ten patients had a history of alcohol abuse; three of these had alcohol withdrawal seizures in addition to non-withdrawal seizures. AEDs were prescribed to 16/21 (76%) subjects, however, non-adherence was noted in five of these subjects. Per EMS report, two SUDEP victims had a witnessed seizure at the time of death. Resuscitation was attempted in 10 cases (table 2).



**Figure 2.** History of mental health disorders in victims of sudden death from any cause. Neurologist-identified cases of SUDEP had a higher prevalence of history of alcohol abuse compared to subjects with other causes of death ( $p < 0.05$ ). SUDEP victims also had a higher prevalence of depression, anxiety disorder, bipolar disorder, and substance abuse, besides alcohol, compared to other groups, however, these results were not significant. One standard error bar is displayed.



**Figure 3.** Average number of outpatient clinic encounters, Emergency Department (ED) encounters, and total encounters per victim. SUDEP victims had slightly less outpatient clinic visits and ED visits compared to other causes of death. These results were not significant. Standard error bars are displayed.

### Non-SUDEP victims with a history of seizure

Of the 35 victims with a history of seizures, six were classified as possible SUDEP and eight were non-SUDEP. Of these 14 cases, nine of these deaths were attended by a medical examiner. Cause of death

was listed as cardiac ( $n=5$ ; one with ischaemic heart disease, two with atherosclerotic disease, one with heart failure, and one with cardiac dysrhythmia), respiratory ( $n=3$ ; one with flu-like illness, one with respiratory failure, and one with asthma), multiple sclerosis (one patient), diabetes mellitus I (one patient),

**Table 2.** Classification of SUDEP among victims of sudden death from any cause with a history of seizures in Wake County, North Carolina who died between March 1, 2013 and February 28, 2015.

<b>SUDEP victims (Definite and Probable SUDEP) n=21 (n [%])</b>	
SUDEP identified by death certificate	6 (29%)
Physician-signed death certificate	1/6 (17%)
Medical examiner-signed death certificate	5/6 (83%)
Age (mean, [SD])	51.24 (11.3)
Male	11 (52%)
White	12 (57%)
Witnessed seizure at time of death	2 (10%)
Resuscitation attempted	10 (48%)
History of stroke	1 (5%)
History of traumatic brain injury	2 (10%)
History of alcohol abuse	10 (48%)
Alcohol withdrawal seizures	3 (33%)
Cerebral palsy	2 (10%)
Antiepileptic medications prescribed	16 (76%)
Non-compliance noted	5 (31%)

hypertensive chronic kidney disease (one patient), intracerebral haemorrhage associated with cocaine use (one patient), and alcohol abuse (two patients). A history of coronary artery disease (33%), diabetes mellitus (33%), dyslipidaemia (33%), chronic kidney disease (19%), chronic respiratory disease (43%), and metabolic syndrome (19%) was common in these patients.

## Discussion

Our findings confirm that patients with epilepsy have a markedly increased risk of sudden death and that SUDEP, seizures, and complications of seizures remain under-reported as the cause of death. Definite and Probable SUDEP accounted for 5.3% of sudden deaths in our population-based, out-of-hospital cohort. If Possible SUDEP cases are included, this increases to 6.8% of the cohort. Previous studies report that SUDEP accounts for 8-17% of deaths in people with epilepsy (Téllez-Zenteno *et al.*, 2005). While the prevalence of epilepsy is 1% in the general population, we found the frequency of SUDEP to be much higher among

sudden deaths. Our findings parallel a recent prospective, population-based study of sudden cardiac deaths in San Francisco County, where 18/25 epilepsy patients had Definite or Possible SUDEP (Devinsky *et al.*, 2017). As in our study, only a minority of SUDEP cases adjudicated by an academic adjudication committee were identified by a medical examiner or death certificate. For epilepsy patients who die suddenly, the possibility of SUDEP should be carefully considered and alternative causes (e.g. cardiac arrest or myocardial infarction, drug intoxication) should be supported by evidence beyond pathological or toxicological findings commonly seen in the demographically-matched population.

One of our study objectives was to characterize SUDEP victims and identify potential risk factors for SUDEP. We expected that SUDEP victims would be qualitatively different from other sudden death victims. We expected them to have less cardiovascular and other chronic disease risk factors, but more indicators of social and medical isolation. We found that SUDEP cases were significantly more likely to have a history of alcohol abuse than non-SUDEP cases. We did not find differences in other demographic features or healthcare utilization between SUDEP and non-SUDEP cases, although, to some degree, this may have reflected the limited sample size and high variance. For example, the average number of health care visits during the two years before death was 2.75-fold lower for the SUDEP cases than non-SUDEP controls. However, the overall low level of healthcare utilization may reflect our catchment area, as victims of sudden death were medically and socially isolated (Adabag *et al.*, 2010). This is supported by our finding that 90% of all SUDEPs and non-SUDEPs were unwitnessed. Further, 14% of SUDEP victims lived in a census tract where the income level was designated as low, compared to 9% of the general Wake County, NC population. The psychosocial burden of epilepsy may also contribute to medical and social isolation. Alcohol abuse was more prevalent in SUDEP victims compared to non-SUDEP victims. SUDEP victims commonly had mental health disorders including depression, schizophrenia, anxiety, bipolar disorder, and a history of substance abuse besides alcohol. These mental health disorders may pose additional barriers to appropriate medical care, which can help explain the decreased level of healthcare utilization in the SUDEP group (Hert *et al.*, 2011).

The SUDEP cases in our study did not receive optimal care. Many epilepsy patients, especially those from lower income groups, have limited access to the most effective medical and surgical therapies (Burneo *et al.*, 2009). Seizure monitoring and advice are sub-optimal from both general practitioners' and patients' perspectives (Risdale *et al.*, 1996). General practitioners often feel they lack adequate resources and

knowledge to properly diagnose epilepsy (Thapar, 1998). Yet, ~35% of non-institutionalized epilepsy patients do not receive care from a neurologist or epilepsy specialist, despite better seizure control with specialty care from an epileptologist compared to other neurologists (Szaflarski *et al.*, 2008). Poor seizure control is associated with an increased risk of SUDEP (Hesdorffer *et al.*, 2011). Remarkably, none of our SUDEP victims visited the neurology department in the two years before death. Further, 24% of SUDEP victims were not prescribed antiepileptic medications, and 29% of our SUDEP victims with prescribed AEDs were non-adherent for these medications. Only one SUDEP victim had therapeutic levels of AEDs at post-mortem (12 mg/L levetiracetam). This is greater than the non-compliance rate reported in earlier studies on living patients with seizures (Kobau *et al.*, 2005). The high frequency of mental health disorders (figure 3) and low level of healthcare utilization and medication adherence together suggests epilepsy care was poor in our SUDEP patients. Elevated mortality rates in epilepsy patients from lower socioeconomic regions with psychiatric comorbidities has been well documented (Fazel *et al.*, 2013; Kaiboriboon *et al.*, 2014). Discussion about SUDEP and its potential risk factors early during the course of a patient's epilepsy diagnosis is essential (Shankar *et al.*, 2017). Death certificates are the mainstay to survey for sudden death in epilepsy patients. However, our data as well as others suggest that death certificates underestimate the frequency of SUDEP (Schraeder *et al.*, 2006; Atherton *et al.*, 2017). In our population, "seizures" or "complications of seizures" were listed as the primary cause of death on the death certificate in six victims, compared to 21 neurologist-identified Definite and Probable SUDEP cases. This suggests that seizure disease is considered as the primary cause of death on death certificates in less than 30% of neurologist-identified SUDEP among seizure victims, with an even smaller percentage if Possible SUDEP cases are included. However, it should be noted that "SUDEP" was never explicitly stated on the death certificate. Cardiac causes of death were commonly listed on death certificates despite the prevalence of cardiac comorbidities being lower in SUDEP victims than in non-SUDEP victims. This may suggest that the role of cardiac causes of death was overestimated, when in fact, epilepsy was the underlying cause of death. Systematic interviews with next-of-kin or significant others to ascertain a possible history of seizures or epilepsy should be performed in all cases of sudden death. Further, examination of medical records and autopsy reports are critical to accurately identify SUDEP cases due to the limited accuracy of death certificates.

## Limitations

Our study has several limitations. The rate of autopsy was only 19% overall and 24% for SUDEP victims, limiting identification of other potential competing causes of death. Additionally, despite rigorous attempts to gather medical records, these were lacking for 129 (32%) sudden death victims, and only death certificates were available for 28 (7%). This made determination of epilepsy history and neurologist-adjudication of SUDEP difficult. Further, a history of epilepsy, medical disorders, mental health disorders, and alcohol abuse are likely to be under-reported in the available medical records, as well as by medical examiners relying on these records and next-of-kin who may be impossible to find or have limited knowledge of the patient's medical history (Hopkins *et al.*, 1994; Takayanagi *et al.*, 2014). Our small sample size limited study power. Finally, because our study was cross-sectional and retrospective, we could not assess the temporal relationship between the variables of interest.

Despite these limitations, we were able to rigorously analyse all records available including EMS reports, post-mortem examinations including medical examinations, complete autopsies, toxicology reports, and full medical records from hospitals and other providers. Our findings highlight the high risk of SUDEP among epilepsy patients who die suddenly, and the demographic diversity of our cohort suggests that these results are generalizable to other areas.

## Conclusion

SUDEP is a frequent and under-reported cause of mortality among people with epilepsy, and death certificates do not accurately identify these deaths. Alcohol abuse was more common among sudden death in epilepsy victims than other victims of sudden death. Additionally, mental health disorders, medication non-compliance, and poor contact with healthcare were common among these victims. Better surveillance methods and targeted prevention (e.g. patient and physician education about SUDEP risk factors and the importance of antiepileptic drug adherence, adequate sleep, and limited or no alcohol) and intervention programmes (e.g. currently unproven, seizure detection devices that may alarm others to nocturnal seizures) could reduce the burden of SUDEP. Targeted programmes should also improve access to neurological and psychiatric care, prevention and treatment of substance abuse, and patient engagement with their health in addition to promoting healthy lifestyles in those with epilepsy. □

## Supplementary data.

Summary didactic slides are available on the [www.epilepticdisorders.com](http://www.epilepticdisorders.com) website.

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None of the authors have any conflict of interest to declare.

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## TEST YOURSELF



- (1) How common is sudden unexpected death in epilepsy (SUDEP) among sudden death cases aged 18-64?
- (2) What are the demographic and clinical characteristics of SUDEP cases aged 18-64?
- (3) How accurate are death certificates in capturing SUDEP?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com), under the section "The EpiCentre".*