Published Ahead of Print on June 7, 2017 as 10.1212/WNL.0000000000004094

The incidence of SUDEP

A nationwide population-based cohort study

Olafur Sveinsson, MD
Tomas Andersson, BSc
Sofia Carlsson, PhD
Torbjörn Tomson, MD

Correspondence to
Dr. Sveinsson:
olafur.sveinsson@karolinska.se

ABSTRACT

Objective: To identify all cases of sudden unexpected death in epilepsy (SUDEP) among people in Sweden during 1 year and to determine the SUDEP incidence in relation to age, sex, and psychiatric comorbidity.

Methods: We included all individuals with a hospital-based ambulatory care or hospital discharge diagnosis of epilepsy in the Swedish National Patient Registry during 1998–2005 who were alive on January 1, 2008. Deaths during 2008 were identified by linkage to the National Cause of Death Registry. Death certificates, medical charts, and police and autopsy reports were extensively reviewed to identify SUDEP cases.

Results: Of 57,775 epilepsy patients alive on January 1, 2008, 1,890 died (3.3%) during 2008. Of these, 99 met the Annegers SUDEP criteria (49 definite, 19 probable, and 31 possible). SUDEP accounted for 5.2% of all deaths and 36% of deaths in the 0–15 years age group. The incidence of definite/probable SUDEP was 1.20/1,000 person-years, and higher in men (1.41) than in women (0.96). All SUDEP cases <16 years were in boys. SUDEP incidence at ages <16, 16–50, and >50 years was 1.11, 1.13, and 1.29, respectively, per 1,000 person-years. The incidence was 5-fold increased among female patients with psychiatric comorbidities compared to those without. Epilepsy was mentioned on the death certificate in only 62 of the 99 (63%) SUDEP cases.

Conclusions: Methods relying on death certificates underestimate SUDEP incidence. SUDEP risk has been underestimated especially in boys and in older people regardless of sex. Patients with psychiatric comorbidities, women in particular, are at increased SUDEP risk. ***Neurology*®** **2017;89:1–8**

GLOSSARY

CI = confidence interval; **ICD** = *International Classification of Diseases*; **SNPR** = Swedish National Patient Register; **SUDEP** = sudden unexpected death in epilepsy.

The risk of sudden unexpected death has been estimated to be 24- to 28-fold higher among young people with epilepsy than in the general population,[1,2] adding considerably to the burden of young persons with epilepsy. The public health burden of sudden unexpected death in epilepsy (SUDEP) was recently assessed based on a systematic review of epidemiologic studies.[3] The crude annual incidence of SUDEP was estimated to 1.16 (0.95–1.36) per 1,000 persons with epilepsy, and in terms of potential years of life lost, SUDEP ranked second only to stroke among neurologic diseases.[3] Estimates were based on 3 population-based studies where SUDEP cases were ascertained through medical examiner, coroner, or hospital postmortem registers in the United States or United Kingdom, and SUDEP incidence was calculated based on a presumed prevalence of epilepsy.[4–6]

However, due to methodologic limitations in previous studies, estimates of the incidence of SUDEP are uncertain and rates have varied substantially.[7,8] Limitations include few cases in each study; unclear SUDEP criteria; case ascertainments with considerable risk of missing SUDEP cases[4–6,9]; limited geographic areas, where representativeness is uncertain[4–6,10,11]; and presumed

Editorial, page XXX

Supplemental data at Neurology.org

From the Department of Neurology (O.S., T.T.), Karolinska University Hospital; Department of Clinical Neuroscience (O.S., T.T.) and Epidemiology Unit, Institute of Environmental Medicine (T.A., S.C.), Karolinska Institutet, Stockholm; and Center for Occupational and Environmental Medicine (T.A.), Stockholm County Council, Sweden.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

epilepsy prevalence used to calculate the incidence.[4–6,10] Many studies have also applied age limits[1,9,12,13] to their study populations, preventing a full understanding of the SUDEP spectrum.

We therefore carried out a nationwide, population-based, cohort study of the incidence of SUDEP at all ages. In addition, we aimed at assessing SUDEP risk in relation to psychiatric comorbidity as this has been associated with increased risk of premature death in a previous study of epilepsy.[14]

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committee of Karolinska Institutet.

Study population. The Swedish National Patient Register (SNPR) contains all patients hospitalized (with total national coverage from 1987) or managed in hospital-based ambulatory care (since 2001) in Sweden.[15] The Register has been validated for several diagnoses, and shown a high accuracy,[15] although not yet formally validated for epilepsy. Each individual's outpatient visit or hospital discharge diagnosis (ICD code) is linked with their unique personal identification number. We identified all persons who at some point during 1998–2005 were registered in the SNPR with an ICD-10 code for epilepsy (G 40) (n = 78,424). The present study of the incidence of SUDEP is based on an in-depth assessment of all deaths during 1 year: 2008. The study population consists of all individuals who were alive on January 1, 2008 (n = 57,775), and we retrieved death certificates for everyone who died during 2008 (n = 1,890) (figure 1). The SNPR was also used to identify those in the epilepsy study population who had psychiatric comorbidity registered during 1998–2005 (ICD-10 code F 00-99).

Identification of SUDEP. All death certificates were reviewed by one neurologist (O.S.). Obvious non-SUDEP deaths such as cancer, terminal illness, postmortem confirmed pneumonia, stroke, or myocardial infarction (figure 1) were excluded from further analysis based on the information in the death certificates. This process considered all information on the death certificate and postmortem results. When SUDEP could possibly be the cause of death, patient records from family physicians, hospital records, nursing homes or other institutions, police records, and autopsy records were reviewed (O.S.) and information was extracted by a standardized protocol. Emphasis was on attaining a doctor or police report regarding circumstances surrounding the death, including documented interviews with eyewitnesses, caregivers, and relatives. All obvious non-SUDEP cases were discarded. Remaining potential SUDEP cases were reviewed by 2 neurologists (O.S. and T.T.) and classification of the cases was made through consensus. A forensic pathologist was consulted in 14 cases where autopsy reports were difficult to interpret in relation to SUDEP criteria.

SUDEP definition and classification. SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom postmortem examination does not reveal a structural or toxicologic cause for death.[16] We classified our SUDEP cases according to 2 different proposals. According to the Annegers criteria,[17] SUDEP cases were divided into 3 subgroups on the basis of the certainty of the diagnosis: (1) definite SUDEP, when all clinical criteria are met, and an autopsy is performed that revealed no alternative cause of death; (2) probable SUDEP, when all clinical criteria are met, but no autopsy is performed; and (3) possible SUDEP, when SUDEP could not be ruled out, but there is insufficient evidence regarding the circumstances of the death and no autopsy is performed.[17] Based on the unified definition of SUDEP proposed by Nashef et al.,[18] cases were divided into the above subgroups with the following modification: when there is a concomitant condition other than epilepsy and if the death may have been due to the combined effect of both conditions, the case is classified as SUDEP Plus, where definite SUDEP Plus otherwise satisfied the definition of definite SUDEP and probable SUDEP Plus satisfied the definition of probable SUDEP. The Nashef classification also includes (1) near SUDEP/near SUDEP Plus, where a patient with epilepsy survives resuscitation for more than 1 hour after a cardiorespiratory arrest that has no structural cause identified after investigation; and (2) unclassified, where incomplete information is available and the death not possible to classify.

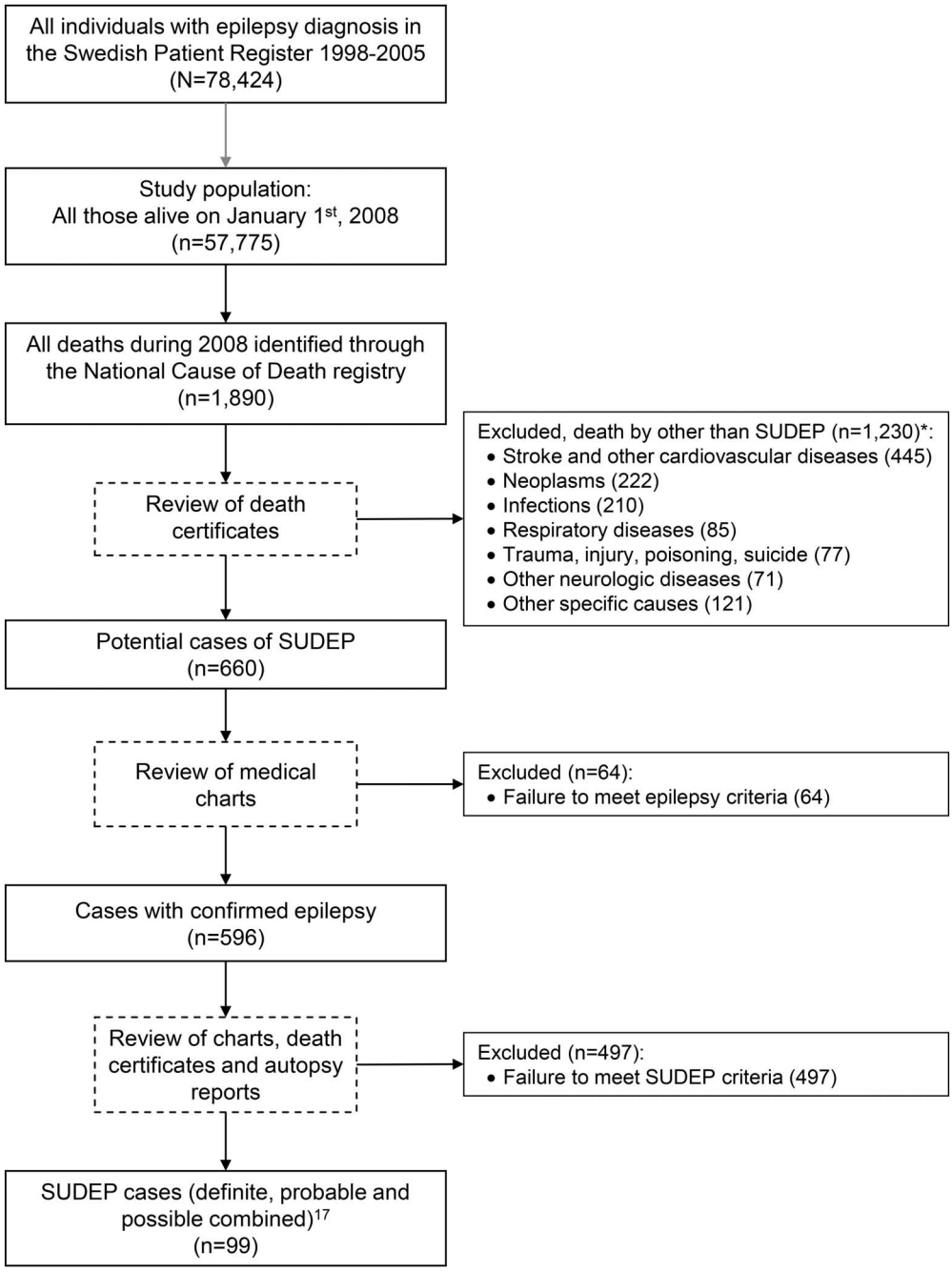
Statistics. Incidence rates were calculated for specific SUDEP definitions with confidence intervals (CIs) constructed by the exact method.[19] We calculated incidence rate ratios comparing male to female patients and individuals with and without psychiatric comorbidities, together with 95% exact CIs.[20] SAS software (version 9.4) (SAS Institute Inc., Cary, NC) for Microsoft (Redmond, WA) Windows was used for all statistical analysis.

RESULTS

Of the 1,890 participants who died during 2008, 1,230 were considered, based on the information on the death certificate, to have had an obvious non-SUDEP death and were not analyzed further (figure 1). Of the 660 potential cases whose records were examined in detail, 64 (9.7%) did not fulfill the epilepsy criteria.[21] After review of the remaining 596 medical charts, autopsy reports, and other sources of information, 99 (67 men) met the Annegers SUDEP criteria (49 definite, 19 probable, and 31 possible) and 96 the updated Nashef criteria (33 definite, 18 definite SUDEP Plus, 18 probable, 3 near SUDEP, and 24 possible). Three deaths were considered unclassifiable according to the Nashef criteria but classified as possible in the Annegers criteria. The interrelationship between the 2 SUDEP classifications is illustrated in table e-1 at Neurology.org. All 49 patients who were classified as definite in the Annegers classification were either classified as definite (n = 33) or definite SUDEP Plus (n = 16) in the Nashef classification. Given the close similarities between on the one hand definite and probable SUDEP according to Annegers and on the other definite, probable, and definite SUDEP plus according to Nashef, we used definite and probable according to Annegers for our calculations of the SUDEP incidence unless otherwise stated.

Demographic data and information on psychiatric comorbidity for the study population, the deceased, as well as the SUDEP cases are summarized in table 1.

Figure 1 Flowchart describes the selection process



*In addition to the underlying causes of death listed here, all supplementary information on death certificates, including contributing causes of death, were considered before designating a case as a non-sudden unexpected death in epilepsy (SUDEP) death.

Each definite and probable SUDEP case according to the Annegers classification is shown by their age at death and sex in figure 2. Figure e-1, which also includes possible cases, illustrates SUDEP cases by 3 age groups showing that the proportion of possible cases increased markedly with age. The relationship between age, sex, and classification according to the 2 methods is provided in table e-2.

Definite and probable SUDEP accounted for 3.6% of all deaths in the study population during 2008, and 5.2% when possible SUDEP was included. The relative contribution of SUDEP (definite, probable, and possible) to overall deaths was 36.0% (9/25) in the age group 0–15 years, 21.3% (34/160) between 16 and 50 years, and 3.3% (56/1,706) above 50 years. SUDEP incidence was 1.20/1,000 person-years (definite/probable according to Annegers), 1.24/1,000, (definite/probable/SUDEP Plus according to Nashef), and 1.74/1,000 if possible SUDEP was included. In the same range in all 3 age groups,

Table 1 Demographic data and occurrence of psychiatric comorbidity in the study population, deceased among the study population, and sudden unexpected death in epilepsy (SUDEP) cases during 2008

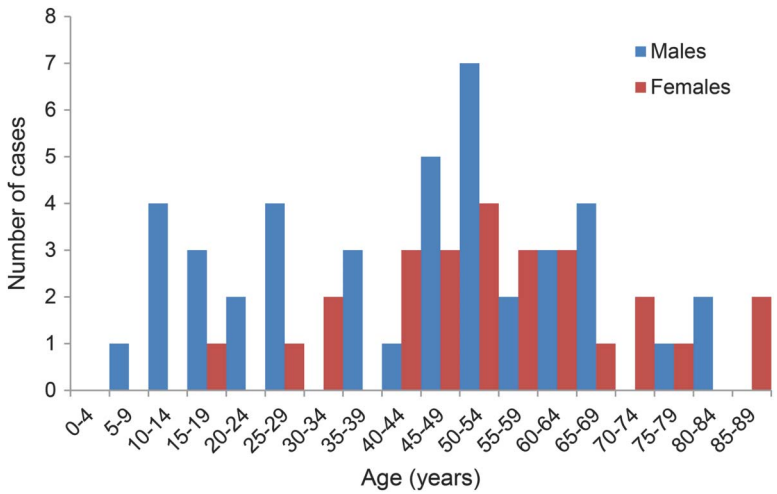
	Study population (n = 57,775)	Deceased during 2008 (n = 1,890)	SUDEP Annegers[a] (n = 68)	SUDEP Nashef[b] (n = 69)
Male/female, n (%)	30,274/27,501 (52/48)	1,055/835 (56/44)	42/26 (62/38)	43/26 (62/38)
Age, y, median (range)	46 (3–106)	Not applicable	Not applicable	Not applicable
Age at death, y, median (range)	Not applicable	78 (4–100)	50 (4–88)	50 (4–88)
Psychiatric comorbidity, n (%)[c]	16,821 (29)	774 (41)	32 (47)	32 (46)
Antiepileptic drug treatment, n	Not applicable	Not applicable	64	65
Monotherapy, n	Not applicable	Not applicable	34	34
Polytherapy, n	Not applicable	Not applicable	30	31
None, n	Not applicable	Not applicable	4	4

[a] Includes definite and probable.[17]
[b] Includes definite, probable, and definite SUDEP Plus.[18]
[c] Any psychiatric diagnosis (F00-F99) during inclusion period (1998–2005). Includes in order of frequency the following ICD-10 blocks: mental and behavioral disorders due to psychoactive substance abuse (F10-F19); neurotic, stress-related, and somatoform disorders (F40-F48); mood (affective) disorders (F32-F39); mental retardation (F70-F79); schizophrenia, schizotypal, and delusional disorders (F20-F29).

the trend was for higher incidence of definite/probable SUDEP among patients older than 50 years (table 2). Incidence was higher in male than in female participants, in particular among children, and this difference was significant when possible SUDEP was included (table 2). Notably, there was no SUDEP case among girls <16 years. Epilepsy type, etiology, and seizure frequency for SUDEP cases <16 years is presented in table e-3. The incidence was higher among those with psychiatric comorbidities compared to those without, in particular among female patients (table 3). The SUDEP incidence rate 2008 in relation to different psychiatric subgroups is shown in table e-4.

Out of the 99 cases with definite, probable, or possible SUDEP, SUDEP was listed as the immediate cause of death on the death certificate in one case only. Seizure was mentioned as the immediate cause in another 18, and epilepsy in 8 cases. Thus SUDEP, seizures, or epilepsy was considered to be the immediate cause of death in 27 out of 99 cases. The total list of immediate causes is provided in figure e-2. Epilepsy was mentioned in any position of the death certificate in 63 (63.6%) of the 99 SUDEP cases and in 287 (15.2%) of the 1,890 individuals who died during 2008.

Figure 2 Age and sex distribution of definite and probable sudden unexpected death in epilepsy cases according to the Annegers classification[17]



DISCUSSION In this nationwide population-based study of SUDEP among all ages, we applied 2 different SUDEP classifications and noted that the overall incidence of SUDEP is very similar between the two. Including definite, probable, and possible SUDEP according to the Annegers criteria, or definite, probable, definite SUDEP Plus, and possible as defined by Nashef et al., the incidence was 1.74 per 1,000 person-years, and 1.20 and 1.24, respectively, with possible excluded. In accordance with previous reports,[4–6] the incidence was higher among male patients. The sex difference was most pronounced in the young age group, with 7 definite/probable cases among boys and none among girls. In contrast to most previous studies,[3,7] we found similar incidence rates of definite/probable SUDEP in all age groups, including in those younger than 16 years as well as those over 50. Most remarkable is the high incidence (2.05 per 1,000 person-years) among boys under 16 years, all of whom had treatment-resistant epilepsy (table e-3). The observed high proportion of possible SUDEP in patients older than 50 is hardly surprising considering the increasing occurrence of competing causes of death as well as lower autopsy rates among older persons. This highlights the difficulties in obtaining a reliable assessment of the SUDEP risk in older people, and our estimates based on definite/probable

Table 2 Age- and sex-specific incidence of sudden unexpected death in epilepsy (SUDEP) according to the Annegers classification.[17]

	All		Male		Female		
	Cases/person-years	I (95% CI)	Cases/person-years	I (95% CI)	Cases/person-years	I (95% CI)	Rate ratio[a] (95% CI)
Definite and probable SUDEP							
All ages	68/56,799	1.20 (0.93–1.52)	42/29,729	1.41 (1.02–1.91)	26/27,071	0.96 (0.63–1.41)	1.47 (0.88–2.50)
<16 y	7/6,310	1.11 (0.45–2.29)	7/3,410	2.05 (0.83–4.23)	0/2,900	—	—
16–50 y	29/25,707	1.13 (0.76–1.62)	17/13,048	1.30 (0.76–2.09)	12/12,658	0.95 (0.49–1.66)	1.37 (0.62–3.15)
>50 y	32/24,783	1.29 (0.88–1.82)	18/13,271	1.36 (0.80–2.14)	14/11,512	1.22 (0.66–2.04)	1.12 (0.52–2.42)
Definite, probable and possible SUDEP							
All ages	99/56,799	1.74 (1.42–2.12)	67/29,729	2.25 (1.75–2.86)	32/27,071	1.18 (0.81–1.67)	1.91 (1.23–3.00)
<16 y	9/6,310	1.43 (0.65–2.71)	9/3,410	2.64 (1.21–5.01)	0/2,900	—	—
16–50 y	34/25,707	1.32 (0.92–1.85)	21/13,048	1.61 (1.00–2.46)	13/12,658	1.03 (0.55–1.76)	1.57 (0.75–3.41)
>50 y	56/24,783	2.26 (1.71–2.93)	37/13,271	2.79 (1.96–3.84)	19/11,512	1.65 (0.99–2.58)	1.69 (0.95–3.11)

Abbreviation: CI = confidence interval.
Incidence rates (I) are per 1,000 person-years.
[a] Comparing male and female participants.

SUDEP should probably be considered to be minimum numbers and suggest a higher incidence than previously thought. Psychiatric comorbidity has been shown to be associated with premature mortality from external causes in people with epilepsy, although SUDEP was not analyzed in that study.[14] We found a more than 2-fold higher SUDEP incidence in those with psychiatric comorbidity compared to those without, and an almost 5-fold difference among female patients (table 3). The numbers did not allow us to determine differences across subgroups of neuropsychiatric comorbidities, but the highest incidence was noted with organic mental disorders (table e-4). Whether the higher incidence among those with psychiatric comorbidity is related to other SUDEP risk factors such as poor seizure control, concurrent medication, or poorer adherence to the prescribed medication is unclear. Finally, our study confirms the difficulties in using death certificates to identify SUDEP cases as the indicated immediate cause of death was SUDEP in only one case, and SUDEP, seizures, or epilepsy together accounted for no more than 27/99 cases.

The main strength of our study lies in it being nationwide and population-based. Considering that the total Swedish population in 2002 was 8.925 million, the 78,524 individuals identified in the SNPR during 1998–2005 most likely represent the vast majority of inhabitants with epilepsy. A further unique strength is the review of all deaths during 1 year, with meticulous assessment of all relevant documentation for all potential SUDEP cases.

Limitations include that we relied on the ICD codes for epilepsy in the SNPR to define the study population. Our review of medical charts of 660 potential cases, however, suggests a high validity, as more than 90% of reviewed individuals had epilepsy. Assuming that the same degree of misdiagnosis applies for the entire study population (which remains to be shown), our estimates of the SUDEP incidence may thus underestimate the incidence by approximately 10%. Another limitation is that our detailed review of all deaths covered 2008, whereas the study population as well as the occurrence of psychiatric comorbidity was defined by a diagnosis in the SNPR anytime between 1998 and 2005. Fatalities from time of inclusion up to December 31, 2007, were thus not included in our analysis, which was restricted to those 57,775 persons alive on January 1, 2008. Likewise, persons with epilepsy onset after December 31, 2005, were not included in our analysis. Hence, we determined the incidence of SUDEP during 1 year in a prevalent epilepsy population and did not follow newly diagnosed patients from epilepsy onset.

Due to convincing evidence of non-SUDEP causes of death on the death certificate, we restricted our comprehensive review of all documents to 660

Table 3 Sex-specific incidence of sudden unexpected death in epilepsy (SUDEP) according to the Annegers classification[17] in epilepsy patients with and without psychiatric comorbidity

	All		Male		Female		
	Cases/person-years	I (95% CI)	Cases/person-years	I (95% CI)	Cases/person-years	I (95% CI)	Rate ratio[a] (95% CI)
Definite and probable SUDEP							
Without psychiatric comorbidity	36/40,364	0.89 (0.62–1.23)	27/20,561	1.31 (0.87–1.91)	9/19,802	0.45 (0.21–0.86)	2.89 (1.32–6.98)
With psychiatric comorbidity	32/16,426	1.95 (1.33–2.75)	15/9,157	1.64 (0.92–2.70)	17/7,268	2.34 (1.36–3.74)	0.70 (0.33–1.49)
Rate ratio[b] (95% CI)		2.18 (1.31–3.62)		1.25 (0.62–2.43)		5.15 (2.17–13.10)	
Definite, probable, and possible SUDEP							
Without psychiatric comorbidity	50/40,364	1.24 (0.92–1.63)	36/20,561	1.75 (1.23–2.42)	14/19,802	0.71 (0.39–1.19)	2.48 (1.30–4.97)
With psychiatric comorbidity	49/16,426	2.98 (2.21–3.94)	31/9,157	3.39 (2.30–4.81)	18/7,268	2.48 (1.47–3.91)	1.37 (0.74–2.59)
Rate ratio[b] (95% CI)		2.41 (1.59–3.64)		1.93 (1.16–3.22)		3.50 (1.65–7.61)	

Abbreviation: CI = confidence interval.
Incidence rates (I) are per 1,000 person-years.
[a] Comparing male and female participants.
[b] Comparing individuals with and without psychiatric comorbidity.

individuals. We cannot exclude the possibility of missing a few SUDEP cases in this procedure. But should this be the case, they would most likely have been possible SUDEPs due to competing causes of death and thus not have altered our estimates of the incidence of definite and probable SUDEP. A further limitation of our study is the rather small number of cases, hampering subgroup analysis.

In terms of study design, a nationwide Danish study of SUDEP in the young is the one most similar to ours, using Danish health registers to define the epilepsy study population, and review of death certificates to identify SUDEP cases.[1] There are, however, important differences: The Danish study was restricted to ages 1–35 years. Furthermore, the occurrence of SUDEP was determined based on review of death certificates and autopsy records, but not including medical charts, as in our study. Our results, with SUDEP, seizures, or epilepsy listed as the immediate cause of death in only 27% of SUDEP cases, and epilepsy mentioned in any position on the death certificate in 63.6%, clearly show the risk of underestimation of SUDEP incidence with this approach, possibly contributing to the lower incidence of definite and probable SUDEP, 0.41 (0.32–0.55) per 1,000 person-years, in the Danish study.

In previous population-based studies including all age groups, the estimated incidence of definite and probable SUDEP ranged from 0.33 to 1.35 per 1,000 person-years.[2,4–6,8,10–12,22] The wide range could depend on methodologic differences in terms of study populations, SUDEP criteria, and not least for identification of SUDEP cases, in some based on coroner or medical examiners,[4–6] some based mostly on death certificates.[1] Despite some differences in methodology, our observed incidence of 1.20 (0.93–1.52) per 1,000 person-years is similar to the rate of 1.16 (0.95–1.36) reported in a pooled analysis[3] of 3 high-quality population-based studies.[4–6] However, our findings of similar incidence rates across age groups including children and people above 50 years of age differ markedly from what has been reported in the past.[3,23–25] Our incidence rate of 1.11 (0.45–2.29) <16 years of age is considerably higher than 0.20 and 0.43 per 1,000 reported in 2 community-based studies of children with epilepsy,[24–26] and the 0.33 per 1,000 person-years reported in a pooled analysis of 4 cohorts of childhood onset epilepsy.[26] While our data in children should be interpreted with caution considering the small numbers, our comprehensive approach where we review all possible sources of information to identify people with epilepsy, and the cause of their deaths, provides more complete data. The fact that all SUDEP cases in the young age group were in boys is intriguing. We have no explanation but this observation should prompt further studies. All SUDEP children had refractory focal epilepsy, most with frequent generalized tonic-clonic seizures (table e-3), which highlights the importance of early consideration of epilepsy surgery for children to possibly prevent this outcome. Despite the refractory nature of all the cases and some having an epileptic encephalopathy, there was no Dravet case among them. Importantly, in children with epilepsy, the relative contribution of SUDEP to the overall mortality was no less than 36%, compared to 21% in ages 16–50 and only 3% among epilepsy patients above 50 years of age. The lower relative contribution

in higher age groups is evidently due to mortality from other causes becoming more frequent with increasing age. Nevertheless, SUDEP risk in the older age group is higher than previously thought. Our results thus corroborate the opinion of Thurman et al.[3] and Devinsky et al.[27] that the undercount of SUDEP might be great in older age groups. In fact, it is possible that our rates based on definite and probable SUDEP underestimate the risk given the substantially greater number of possible SUDEP cases in the higher age group (figure e-1). Our current experience is that there is less information and documentation to be found regarding the circumstances of death in the older age groups compared to the younger, which likely contributes to underascertainment.

Being nationwide and population-based, our results are truly representative for the incidence of SUDEP in the Swedish prevalent epilepsy population. We can only assume that they are generalizable to other countries with similar living conditions and health care. Our novel findings of significant SUDEP risk for children, in particular boys, for older people, and for women with psychiatric comorbidities need to be confirmed. The findings should, however, be taken into account in the important individualized patient counseling about epilepsy and its associated risks. More research into risk factors for SUDEP is urgently needed. We are currently extending the review of deaths in our study population to cover more years. This will increase the number of SUDEP cases and allow for a case-control study where we will compare characteristics of SUDEP cases to living epilepsy controls in detail.

AUTHOR CONTRIBUTIONS

All authors contributed to study design, analysis, and interpretation of data. O.S. was responsible for collecting data and O.S. and T.T. for review of SUDEP case data. T.A. was responsible for the statistical analysis. All authors contributed to the writing of the manuscript.

STUDY FUNDING

The study was supported by Stockholm County Council.

DISCLOSURE

O. Sveinsson has received grants from GSK, personal fees from Biogen, and other support from Biogen and UCB, outside the submitted work. T. Andersson and S. Carlsson report no disclosures relevant to the manuscript. T. Tomson is associate editor of *Epileptic Disorders* and has received speaker's honoraria to his institution from Livanova, Eisai, UCB, and BMJ India, honoraria to his institution for advisory boards from UCB and Eisai, and research support from Stockholm County Council, CURE, GSK, Bial, UCB, Novartis, and Eisai. Go to Neurology.org for full disclosures.

Received January 23, 2017. Accepted in final form March 22, 2017.

REFERENCES

1. Holst AG, Winkel BG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 2013;54:1613–1620.
2. Ficker DM, So EL, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998; 51:1270–1274.
3. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55:1479–1485.
4. Leestma JE, Kalelkar MB, Teas SS, Jay GW, Hughes JR. A prospective study on sudden unexpected death in epilepsy. Ann Neurol 1989;26:195–203.
5. Langan Y, Nolan N, Hutchinson M. The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow. Seizure 1998;7:355–358.
6. Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Seizure 2003;12:456–464.
7. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016;15:1075–1088.
8. Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2017;58: 17–26.
9. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet 1999;353:888–893.
10. Aurlien D, Larsen JP, Gjerstad L, Taubøll E. Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case-control study. Epilepsia 2012; 53:258–266.
11. Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. Lancet Neurol 2006;5:481–487.
12. Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. Epilepsia 1995;36:29–36.
13. Langan Y, Nashef L, Sander JW. Certification of deaths attributable to epilepsy. J Neurol Neurosurg Psychiatry 2002;73:751–752.
14. Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013; 382:1646–1654.
15. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
16. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997;38(suppl 11): S6–S8.
17. Annegers IF. United States perspective on definitions and classifications. Epilepsia 1997;38(suppl 11):S9–S12.
18. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227–233.
19. Garwood F. Fiducial limits for the Poisson distribution. Biometrika 1936;28:437–442.
20. Sahai H, Kurshid A. Statistics in Epidemiology: Methods Techniques and Applications. Boca Raton, FL: CRC Press; 1996.

21. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52:2–26.
22. Ackers R, Besag FM, Hughes E, Squier W, Murray ML, Wong IC. Mortality rates and causes of death in children with epilepsy prescribed antiepileptic drugs: a retrospective cohort study using the UK General Practice Research Database. Drug Saf 2011;34:403–413.
23. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150–1159.
24. Donner EJ, Smith CR, Snead OC III. Sudden unexplained death in children with epilepsy. Neurology 2001;57:430–434.
25. Weber P, Bubl R, Blauenstein U, Tillmann BU, Lutschg J. Sudden unexplained death in children with epilepsy: a cohort study with an eighteen-year follow-up. Acta Paediatr 2005;94:564–567.
26. Berg AT, Nickels K, Wirrell EC, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics 2013;132:124–131.
27. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. Neurology 2016;86:779–786.